COUNTWAY LIBRARY
HC 3IHX E

BOSTON MEDICAL LIBRARY
IN THE
FRANCIS A. COUNTWAY
LIBRARY OF MEDICINE

Digitized by the Internet Archive
in 2016

https://archive.org/details/westernjournalof1464cali

INCORPORATING
ARIZONA MEDICINE
SEE PAGE 430

# The Western Journal of Medicine

DISPLAY SHELVES

VOLUME 146 • NUMBER 4 APRIL 1987

**CLINICAL INVESTIGATION**

431 Blue-Yellow Vision Deficits in Patients With Diabetes
M ROCKETT, D ANDERLE and A N BESSMAN

**CLINICAL MEDICINE**

434 Evaluation and Treatment of Smell Dysfunction
T M DAVIDSON, A JALOWAYSKI, C MURPHY and R D JACOBS

439 Absence of HIV Antibody Among Dental Professionals Exposed to Infected Patients
N M FLYNN, S M POLLET, J R VAN HORNE, R ELVEBAKK, S D HARPER and J R CARLSON

**CLINICAL REVIEW**

443 Laboratory Evaluation of Anemia
R O WALLERSTEIN, Jr

**MEDICAL PROGRESS**

452 Clinical Evaluation and Management of Transient Ischemic Attacks
J F ROTHROCK

**MEDICAL STAFF CONFERENCE**

461 Current Concepts in the Treatment of Tuberculosis
Discussant: I B TAGER

**EPITOMES**

466 Important Advances in Orthopedics

**EDITORIALS**

471 Health Care in a Dreamworld • Diagnosis and Treatment of Smell and Taste Disorders • Clinical Evaluation of Anemia • Transient Ischemic Attacks • It Can Be a Lethal Instrument

**CASE REPORTS**

476 Myasthenia Gravis and Hyperthyrotropinemia in a Child
S M SCOTT, A H KLEIN and J A BRASEL

479 *Streptococcus sanguis II* (Viridans) Prosthetic Valve Endocarditis With Myocardial, Splenic and Cerebral Abscesses
S G YOUNG, T DAVEE, J FIERER and M K MOREY

481 Sarcoidosis Presenting as Chronic Thrombocytopenia
S K FIELD and M-C POON

482 Atypical Diffuse Angiosarcoma of the Liver
G C KANEL, J KORULA, C T LIEW and R L PETERS

**CORRESPONDENCE**

486 Addendum to Living Will • Cost-Effectiveness of Fecal Occult Blood Screening • Was It Worth It? • Natural Death Acts • Cognitive-Procedural Differences • Illness From Organophosphate Exposure • Educating the Public About Life-Style and Nutritional Practices • Healing the Healers • Correction: Common AIDS-Related Problems

**TOPICS IN PRIMARY CARE MEDICINE**

490 Screening in Preventive Care for Adolescents
P BRAVEMAN and K E TOOMEY

**HEALTH CARE DELIVERY**

494 Physicians as Patients—The Use of Obstetric Technology in Physician Families
C E DUGOWSON and S K HOLLAND

**PUBLIC HEALTH AND PREVENTIVE MEDICINE**

497 Injuries and Fatalities Associated With Off-Road Three-Wheeled All-Terrain Vehicles
C M SEWELL, J S PINE and H F HULL

**ALTERNATIVE FORMS OF THERAPY**

499 Using Resistant Behaviors in the Treatment of Alcoholic Patients
L M CRAWLEY

**IN THE FOREFRONT**

502 Teaching Spanish and Cross-cultural Sensitivity to Medical Students
T GONZALEZ-LEE and H J SIMON

**INFORMATION**

505 Nailing Down the Cause of Periungual Lesions
H SCHNEIDERMAN and A L PARKE

**OTHER FEATURES**

423 Books Received
424 Western Continuing Medical Education Activities
433 Book Review
451 Software Review
498 Medical Practice Question
513 In Memoriam
525 Classified Advertising
529 Subscription Information
534 Western State Medical Associations' Meetings

**Detailed Table of Contents:** 405, 409, 416

THE FRANCIS A. COUNTWAY LIBRARY OF MEDICINE BOSTON, MA APR 30 1987

Official Journal of the Arizona Medical Association, the California Medical Association, the Idaho Medical Association, the Montana Medical Association, the Nevada State Medical Association, the New Mexico Medical Society, the Utah State Medical Association, the Washington State Medical Association and the Wyoming Medical Society. Affiliated Specialty Society: California Society of Internal Medicine.

Affiliated Clinical Investigation Societies: the Western Association of Physicians; the Western Society for Clinical Investigation; the Western Section, American Federation for Clinical Research; the Western Society for Pediatric Research; the Western Region, Society for Investigative Dermatology.

# A million and 1

## A poetic understatement

The actual number is in the billions. For more than 15 years, Dalmane (flurazepam HCl/Roche) has been providing sleep that satisfies patients—sleep that comes quickly and lasts through the night.[1-8]

Sleep that satisfies *you*—you can count on an exceptionally wide margin of safety.[7-9] As always, caution patients about driving or drinking alcohol.

ROCHE®

Copyright © 1986 by Roche Products Inc. All rights reserved

# nights of sleep...

## DALMANE®

brand of
flurazepam HCl/Roche Ⓥ

## sleep that satisfies

Please see adjacent page for references and summary of product information.

**References: 1.** Kales J, *et al: Clin Pharmacol Ther 12*:691-697, Jul-Aug 1971 **2.** Kales A, *et al: Clin Pharmacol Ther 18*:356-363, Sep 1975 **3.** Kales A, *et al: Clin Pharmacol Ther 19*:576-583, May 1976 **4.** Kales A, *et al. Clin Pharmacol Ther 32*:781-788, Dec 1982 **5.** Frost JD Jr, DeLucchi MR: *J Am Geriatr Soc 27*:541-546, Dec 1979 **6.** Dement WC, *et al: Behav Med*, pp 25-31, Oct 1978 **7.** Kales A, Kales JD: *J Clin Psychopharmacol 3*:140-150, Apr 1983 **8.** Tennant FS, *et al*: Symposium on the Treatment of Sleep Disorders, Teleconference, Oct 16, 1984 **9.** Greenblatt DJ, Allen MD, Shader RI: *Clin Pharmacol Ther 21*:355-361, Mar 1977

**DALMANE®**
brand of
flurazepam HCl/Roche ℞
**sleep that satisfies**
15-mg/30-mg capsules

**Before prescribing, please consult complete product information, a summary of which follows:**
**Indications:** Effective in all types of insomnia characterized by difficulty in falling asleep, frequent nocturnal awakenings and/or early morning awakening, in patients with recurring insomnia or poor sleeping habits; in acute or chronic medical situations requiring restful sleep. Objective sleep laboratory data have shown effectiveness for at least 28 consecutive nights of administration. Since insomnia is often transient and intermittent, prolonged administration is generally not necessary or recommended. Repeated therapy should only be undertaken with appropriate patient evaluation.
**Contraindications:** Known hypersensitivity to flurazepam HCl; pregnancy. Benzodiazepines may cause fetal damage when administered during pregnancy. Several studies suggest an increased risk of congenital malformations associated with benzodiazepine use during the first trimester. Warn patients of the potential risks to the fetus should the possibility of becoming pregnant exist while receiving flurazepam. Instruct patients to discontinue drug prior to becoming pregnant. Consider the possibility of pregnancy prior to instituting therapy.
**Warnings:** Caution patients about possible combined effects with alcohol and other CNS depressants. An additive effect may occur if alcohol is consumed the day following use for nighttime sedation. This potential may exist for several days following discontinuation. Caution against hazardous occupations requiring complete mental alertness (*e.g.*, operating machinery, driving). Potential impairment of performance of such activities may occur the day following ingestion. Not recommended for use in persons under 15 years of age. Withdrawal symptoms rarely reported. Abrupt discontinuation should be avoided with gradual tapering of dosage for those patients on medication for a prolonged period of time. Use caution in administering to addiction-prone individuals or those who might increase dosage.
**Precautions:** In elderly and debilitated patients, it is recommended that the dosage be limited to 15 mg to reduce risk of oversedation, dizziness, confusion and/or ataxia. Consider potential additive effects with other hypnotics or CNS depressants. Employ usual precautions in severely depressed patients, or in those with latent depression or suicidal tendencies, or in those with impaired renal or hepatic function.
**Adverse Reactions:** Dizziness, drowsiness, lightheadedness, staggering, ataxia and falling have occurred, particularly in elderly or debilitated patients. Severe sedation, lethargy, disorientation and coma, probably indicative of drug intolerance or overdosage, have been reported. Also reported: headache, heartburn, upset stomach, nausea, vomiting, diarrhea, constipation, GI pain, nervousness, talkativeness, apprehension, irritability, weakness, palpitations, chest pains, body and joint pains and GU complaints. There have also been rare occurrences of leukopenia, granulocytopenia, sweating, flushes, difficulty in focusing, blurred vision, burning eyes, faintness, hypotension, shortness of breath, pruritus, skin rash, dry mouth, bitter taste, excessive salivation, anorexia, euphoria, depression, slurred speech, confusion, restlessness, hallucinations, and elevated SGOT, SGPT, total and direct bilirubins, and alkaline phosphatase and paradoxical reactions, *e.g.*, excitement, stimulation and hyperactivity.
**Dosage:** Individualize for maximum beneficial effect. *Adults:* 30 mg usual dosage, 15 mg may suffice in some patients. *Elderly or debilitated patients:* 15 mg recommended initially until response is determined.
**Supplied:** Capsules containing 15 mg or 30 mg flurazepam HCl.

ROCHE®
Roche Products Inc
Manati, Puerto Rico 00701

***The Western Journal of Medicine***
(ISSN 0093-0415/USPS 084 480) is published monthly for $30 per year (USA and Canada) by the California Medical Association, 44 Gough Street, San Francisco, CA 94103. Second-class postage paid at San Francisco, CA and additional mailing offices.
**POSTMASTER:** Send address changes to *The Western Journal of Medicine*, Circulation, P.O. Box 7602, San Francisco, CA 94120-7602.

***Moving?***

Please give us six weeks notice and supply your personal reference number.

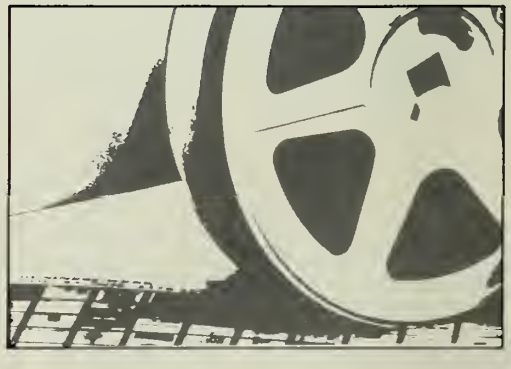
ID No.

The Western Journal of Medicine
P.O. Box 7602
San Francisco, CA 94120-7602.

302703 XX

**The Western Journal of Medicine**
P.O. Box 7602, San Francisco, CA 94120-7602

**This Publication is available in Microform.**



**University Microfilms International**

Please send additional information
for _____
(name of publication)
Name_____
Institution_____
Street_____
City_____
State_____ Zip_____
300 North Zeeb Road, Dept P.R., Ann Arbor, MI 48106

# Un-switch-ables

Patients and physicians alike prefer

**Transderm-Nitro®**
nitroglycerin

Over half a billion* patches prescribed in the U.S. since 1982

The only patch with a rate-limiting membrane

Familiar, distinctive tan color and unique shape recognized by patients everywhere

**There's no substitute for experience**

C I B A

(See Brief Summary of Prescribing Information on the next page.)

*Data on file, CIBA Pharmaceutical Co.

629-7750-A

# Transderm-Nitro®
## nitroglycerin
## Transdermal Therapeutic System

*BRIEF SUMMARY (FOR FULL PRESCRIBING INFORMATION, SEE PACKAGE INSERT)*

**INDICATIONS AND USAGE**
This drug product has been conditionally approved by the FDA for the prevention and treatment of angina pectoris due to coronary artery disease. The conditional approval reflects a determination that the drug may be marketed while further investigation of its effectiveness is undertaken. A final evaluation of the effectiveness of the product will be announced by the FDA.

**CONTRAINDICATIONS**
Intolerance of organic nitrate drugs, marked anemia, increased intraocular pressure or increased intracranial pressure.

**WARNINGS**
In patients with acute myocardial infarction or congestive heart failure, Transderm-Nitro system should be used under careful clinical and/or hemodynamic monitoring.
In terminating treatment of anginal patients, both the dosage and frequency of application must be gradually reduced over a period of 4 to 6 weeks to prevent sudden withdrawal reactions, which are characteristic of all vasodilators in the nitroglycerin class.
Transdermal nitroglycerin systems should be removed before attempting defibrillation or cardioversion because of the potential for altered electrical conductivity which may enhance the possibility of arcing, a phenomenon associated with the use of defibrillators.

**PRECAUTIONS**
Symptoms of hypotension, such as faintness, weakness or dizziness, particularly orthostatic hypotension may be due to overdosage. When these symptoms occur, the dosage should be reduced or use of the product discontinued
Transderm-Nitro system is not intended for immediate relief of anginal attacks. For this purpose occasional use of the sublingual preparations may be necessary.

**ADVERSE REACTIONS**
Transient headaches are the most common side effect, especially when higher doses of the drug are used. These headaches should be treated with mild analgesics while Transderm-Nitro therapy is continued. When such headaches are unresponsive to treatment, the nitroglycerin dosage should be reduced or use of the product discontinued.
Adverse reactions reported less frequently include hypotension, increased heart rate, faintness, flushing, dizziness, nausea and vomiting. These symptoms are attributable to the known pharmacologic effects of nitroglycerin, but may be symptoms of overdosage. When they persist the dose should be reduced or use of the product discontinued. In some patients, dermatitis may occur.

**DOSAGE AND ADMINISTRATION**
Therapy should be initiated with application of one Transderm-Nitro 5 system to the desired area of skin. Many patients prefer the chest; if hair is likely to interfere with system adhesion or removal, it can be clipped prior to placement of the system. Each system is designed to remain in place for 24 hours, and each successive application should be to a different skin area. Transderm-Nitro system should not be applied to the distal parts of the extremities.
The usual dosage is one Transderm-Nitro 5 system every 24 hours. Some patients, however, may require the Transderm-Nitro 10 system. If a single Transderm-Nitro 5 system fails to provide adequate clinical response, the patient should be instructed to remove it and apply either two Transderm-Nitro 5 systems or one Transderm-Nitro 10 system. More systems may be added as indicated by continued careful monitoring of clinical response. The Transderm-Nitro 2.5 system is useful principally for decreasing the dosage gradually, though it may provide adequate therapy for some patients when used alone.
The optimal dosage should be selected based upon the clinical response, side effects, and the effects of therapy upon blood pressure. The greatest attainable decrease in resting blood pressure that is not associated with clinical symptoms of hypotension especially during orthostasis indicates the optimal dosage. To decrease adverse reactions, the size and/or number of systems should be tailored to the individual patient's needs.
Do not store above 86°F (30°C).

**PATIENT INSTRUCTIONS FOR APPLICATIONS**
A patient leaflet is supplied with the systems.

**HOW SUPPLIED**

| Transderm-Nitro System Rated Release *in vivo* | Total Nitroglycerin in System | System Size | Carton Size |
|---|---|---|---|
| 2.5 mg/24 hr | 12.5 mg | 5 $cm^2$ | 30 Systems (NDC 0083-202S-26)<br>*100 Systems (NDC 0083-2025-30) |
| 5 mg/24 hr | 25 mg | 10 $cm^2$ | 30 Systems (NDC 0083-2105-26)<br>*100 Systems (NDC 0083-210S-30) |
| 10 mg/24 hr | 50 mg | 20 $cm^2$ | 30 Systems (NDC 0083-2110-26)<br>*100 Systems (NDC 0083-2110-30) |
| 15 mg/24 hr | 75 mg | 30 $cm^2$ | 30 Systems (NDC 0083-211S-26)<br>*100 Systems (NDC 0083-211S-30) |

*Hospital Pack 100's

C85-35 (Rev 11/85)

**Dist. by:**
**CIBA Pharmaceutical Company**
**Division of CIBA-GEIGY Corporation**
**Summit, New Jersey 07901**

All transdermal nitroglycerin products are being marketed pending final evaluation of effectiveness by the FDA.

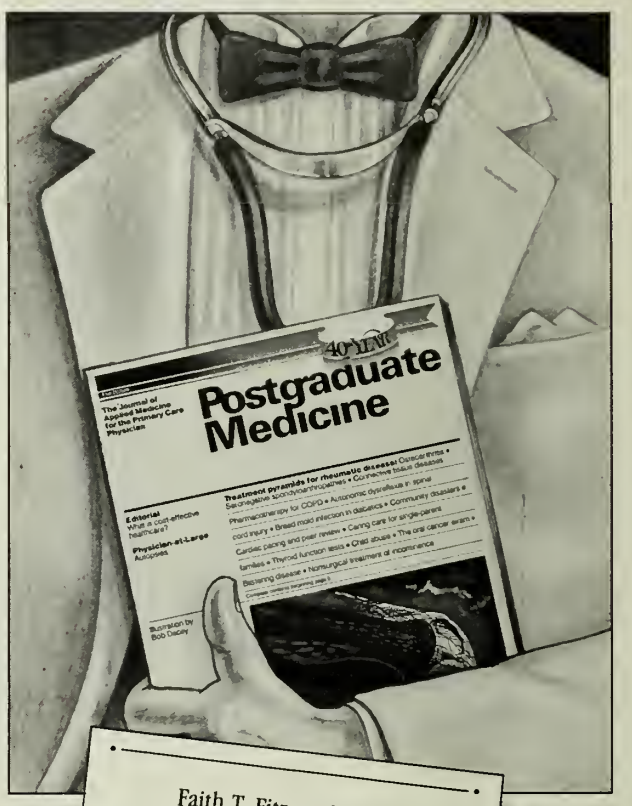
© 1986, CIBA. 629-7750-A

C I B A





# FAMOUS PHYSICIANS ARE SHOWING UP FOR OUR 40th YEAR CELEBRATION.




Faith T. Fitzgerald, M.D.
Richard L. Byyny, M.D.
Frederick C. Goetz, M.D.
Frank A. Finnerty Jr., M.D.
J. Willis Hurst, M.D.
Paul P. Griffin, M.D.

Read Every Issue From Cover to Cover:

**April**
**Symposium:** Focus on General Internal Medicine . . . . . Faith T. Fitzgerald, M.D. coordinator
**Special Article:** General Internal Medicine 1947-1987 . . . . . Richard L. Byyny, M.D.

**May 1**
**Symposium:** Diabetes Mellitus
**Special Article:** Diabetes Mellitus 1947-1987 . . . . . Frederick C. Goetz, M.D.

**May 15**
**Symposium:** Hypertension . . . . . Frank A. Finnerty, Jr. coordinator
**Special Article:** Cardiology 1947-1987 . . . . . J. Willis Hurst, M.D.

**June**
**Symposium:** Orthopedics in Primary Care
**Special Article:** Orthopedics 1947-1987 . . . . . Paul P. Griffin, M.D.

40-YEAR
**Postgraduate Medicine**

***Every Issue is a Celebration of Clinical Information***

# The New Look of
# Medrol® Dosepak™ Unit of Use
## 4 mg methylprednisolone tablets, USP

The explicit printed dosage instructions that accompany each *Dosepak* make it easy for the patient to understand and follow the dosage regimen.

Upjohn 100 A Century of Caring 1886·1986

J-5945RC
January 1986

© 1986 The Upjohn Company

# The Western Journal of Medicine

SINCE 1902

ISSN 0093-0415

PO BOX 7602 • SAN FRANCISCO, CALIFORNIA 94120-7602 • TELEPHONE (415) 863-5522



MALCOLM S. M. WATTS, MD, *Editor*
LLOYD H. SMITH, Jr, MD, *Associate Editor*
DAVID GREER, *Managing Editor*

SALLY LINEBARGER, *Assistant Managing Editor*
SANDRA WILLETT, *Editorial Assistant*

JANICE ANDERSEN, *Copy Editor*
TERESA A. MORRISSEY, *Advertising Production Manager*
FRITZ C. HEATON, *Circulation Coordinator*

editorial communications to DR WATTS • business communications to MR GREER



Official Journal of the Arizona Medical Association, the California Medical Association, the Idaho Medical Association, the Montana Medical Association, the Nevada State Medical Association, the New Mexico Medical Society, the Utah State Medical Association, the Washington State Medical Association and the Wyoming Medical Society.

Affiliated Clinical Investigation Societies: the Western Association of Physicians; the Western Society for Clinical Investigation; the Western Section, American Federation for Clinical Research; the Western Society for Pediatric Research; the Western Region, Society for Investigative Dermatology.

Affiliated Specialty Society: California Society of Internal Medicine.



## EDITORIAL BOARD

*Chairman of the Board*
Malcolm S. M. Watts, San Francisco, Calif

*Associate Editor*
Lloyd H. Smith, Jr, San Francisco, Calif

*Editor for Clinical Investigation*
Kenneth D. Gardner, Jr, Albuquerque, NM

*Special Editor for Arizona*
Marshall B. Block, Phoenix, Ariz

*Special Editor for Idaho*
E. R. W. Fox, Coeur d'Alene, Idaho

*Special Editor for Montana*
Michael R. Oreskovich, Kalispell, Mont

*Special Editor for Nevada*
Dwen C. Peck, Reno, Nev

*Special Editor for New Mexico*
I. Brian Taylor, Carlsbad, NM

*Special Editor for Utah*
John H. Holbrook, Salt Lake City, Utah

*Special Editor for Washington*
David Hopkins, Federal Way, Wash

*Special Editor for Wyoming*
Joseph P. Murphy, Casper, Wyo

*Allergy*
Harold S. Novey, Orange, Calif
Merle S. Scherr, Scottsdale, Ariz

*Anesthesiology*
Ronald D. Miller, San Francisco, Calif

*Cardiac and Thoracic Surgery*
Norman E. Shumway, Stanford, Calif

*Chest Diseases*
Leonard D. Hudson, Seattle, Wash
Thomas L. Petty, Denver, Colo

*Dermatology*
John H. Epstein, San Francisco, Calif
Clark Huff, Denver, Colo
Frank Parker, Portland, Dre
Gerald D. Weinstein, Irvine, Calif

*Emergency Medicine*
William A. Boehm, Alamogordo, NM
W. Richard Bukata, Van Nuys, Calif
Clark Chipman, Portland, Dre
Thomas Elmendorf, Davis, Calif

*General and Family Practice*
Harmon E. Holverson, Emmett, Idaho
Charles W. Huff, Casper, Wyo
Daniel D. Roberts, Central Point, Ore
J. Jerome Wildgen, Kalispell, Mont

*Internal Medicine*
Philip R. Alper, Burlingame, Calif
Robert W. Burroughs, Spokane, Wash
Theodore C. Eickhoff, Denver, Colo
Robert L. Hare, Portland, Dre
Harry R. Kimball, Yakima, Wash
Robert H. Moser, Skokie, Ill
George A. Porter, Portland, Ore
Helen M. Ranney, San Diego, Calif
Laurens P. White, San Francisco, Calif
Ralph C. Williams, Jr, Albuquerque, NM

*Neurology*
J. Richard Baringer, Salt Lake City, Utah
Don F. Seelinger, Albuquerque, NM
W. C. Wiederholt, La Jolla, Calif

*Neurosurgery*
John R. Green, Phoenix, Ariz
George A. Diemann, Seattle, Wash
Charles B. Wilson, San Francisco, Calif

*Nuclear Medicine*
Joseph P. Kriss, Stanford, Calif

*Obstetrics and Gynecology*
Ralph W. Hale, Honolulu, Hawaii
W. LeRoy Heinrichs, Stanford, Calif
Morton A. Stenchever, Seattle, Wash

*Occupational Medicine*
Linda Hawes Clever, San Francisco, Calif

*Ophthalmology*
John L. Keltner, Davis, Calif
Bruce E. Spivey, San Francisco, Calif

*Orthopedics*
Ernest M. Burgess, Seattle, Wash
George E. Omer, Albuquerque, NM

*Otolaryngology*
Roger Boles, San Francisco, Calif
Paul H. Ward, Los Angeles, Calif

*Pathology*
Roy I. Davis, Phoenix, Ariz

*Pediatrics*
Allen W. Mathies, Jr, Pasadena, Calif
William D. Robertson, Seattle, Wash
Arnold L. Smith, Seattle, Wash

*Pharmacology*
Rubin Bressler, Tucson, Ariz

*Physical Medicine and Rehabilitation*
Robert G. Taylor, Sacramento, Calif

*Plastic Surgery*
Richard P. Jobe, Los Altos, Calif
Henry K. Kawamoto, Jr, Santa Monica, Calif

*Preventive Medicine and Public Health*
Joseph L. Lyon, Salt Lake City, Utah
Jonathan Mann, Geneva, Switz

*Psychiatry*
Ralph Crawshaw, Portland, Dre
Alan I. Levenson, Tucson, Ariz
R. Bruce Sloane, Los Angeles, Calif
Joe Paul Tupin, Sacramento, Calif

*Radiology*
M. Paul Capp, Tucson, Ariz
Albert A. Moss, Seattle, Wash
Marshall Rowen, Orange, Calif

*Surgery*
John Wesley Batdorf, Las Vegas, Nev
Daniel T. Cloud, Phoenix, Ariz
Paul A. Ebert, Chicago, Ill
Frank G. Moody, Houston, Tex

*Urology*
Richard Middleton, Salt Lake City, Utah
Thomas A. Stamey, Stanford, Calif

*Senior Members at Large*
Louis K. Diamond, San Francisco, Calif
Edgar Wayburn, San Francisco, Calif

## ADVISORY BOARD, CLINICAL INVESTIGATION

George D. Molnar, Univ of Alberta
Murray A. Katz, Univ of Arizona
Ross E. Petty, Univ of British Columbia
Eldon Shaffer, Univ of Calgary
M. Eric Gershwin, Univ of California, Davis
Jacob Katz, Univ of California, Irvine
Delbert A. Fisher, Univ of California, Los Angeles
Kenneth M. Moser, Univ of California, San Diego
H. Benfer Kaltreider, Univ of California, San Francisco
Alan S. Nies, Univ of Colorado
Irwin J. Schatz, Univ of Hawaii
John Peacock, Univ of Nevada
Sanford Schneider, Loma Linda Univ
Kenneth D. Gardner, Jr, Univ of New Mexico
J. David Bristow, Univ of Oregon
Robert M. McAllister, Univ of Southern California
R. Marvin Bala, Univ of Saskatchewan
Allen D. Cooper, Stanford Univ
Gerald Rothstein, Univ of Utah
David R. Saunders, Univ of Washington

## ADVERTISING INFORMATION

Advertising Sales Representatives

EAST: Saul G. Hornik, SGH, Inc, 12 Court Street, Freehold, NJ 07728 • (201) 972-1911/462-7422
MIDWEST: SGH, Inc, 100 South Wacker Drive, Suite 2030, Chicago, IL 60606 • (312) 782-1100
WEST: Lynne Jeffes, 1340 Paloma Avenue, Burlingame, CA 94010 • (415) 348-747B
CLASSIFIED: PO Box 7602, San Francisco, CA 94120-7602 • Tel: (415) 863-5522/B63-6853

*Advertisements*—The journal is published the first week of the month. Advertising copy must be received no later than the first of the month preceding issue. Advertising rates will be sent on request. Acceptance of advertising is contingent upon approval by the Advertising Committee. *The journal reserves the right to reject any advertisement.*



THE FRANCIS A. COUNTWAY
LIBRARY OF MEDICINE
BOSTON, MA

APR 20 1987



## SUBSCRIPTION INFORMATION

The subscription price per year is $30 in the United States and Canada (US funds); $50 in all other countries. Single copies are $4.50 (which includes postage and handling). Address all subscription communications to:
THE WESTERN JOURNAL OF MEDICINE Circulation, PO Box 7602
San Francisco, CA 94120-7602 • Tel: (415) 863-5522, Ext 245

Allow six weeks for subscriptions to begin. Past issues must be bought individually. So long as reserve stocks are available, missing issue requests from subscribers are honored for up to six months after the issue date. Thereafter, the single copy rate of $4.50 is applicable for each issue available.

*Change of Address*—Requests for change of address should give both the old and new address. Allow six weeks for changeover.


## SUBMITTING MANUSCRIPTS

Manuscripts for consideration should be sent to the editor, Malcolm S. M. Watts, MD, PO Box 7602, San Francisco, CA 94120-7602.

*"Information for Authors"*—A complete guide to manuscript submission and *WJM* style appears in the January and July issues. Manuscripts may be prepared in accordance with the "Uniform Requirements for Manuscripts Submitted to Biomedical Journals" (*British Medical Journal*, June 12, 1982; *Annals of Internal Medicine*, June 1982).

*Author Responsibility*—Authors are responsible for all statements, conclusions and methods of presenting subjects. Articles are accepted on condition that they are contributed solely to this journal.

*Manuscripts*—Ordinarily manuscripts should not exceed 3,000 words (less than 15 typed double-spaced pages). The *original* manuscript and two copies should be submitted, typed double-spaced throughout. If photographic illustrations are desired, three sets of clear, unmounted black and white glossy prints should be supplied. For line drawings, original artwork or glossy prints are acceptable. Tables should be typed on separate sheets of paper.

*Clinical Investigation*—Papers that authors wish considered for the Clinical Investigation section should be so designated in the transmittal letter. Such papers should describe experimental work in humans that extensively and prospectively examines scientific hypotheses relating to disease.


## PUBLISHER

Copyright 1987 by the California Medical Association • Owned and Published by the California Medical Association.

All material subject to this copyright appearing in THE WESTERN JOURNAL OF MEDICINE may be photocopied for the noncommercial purpose of scientific or educational advancement. Volumes begin with January and July.

POLICY COMMITTEE
Frederick S. Armstrong
Laurens P. White
Richard F. Corlin
Charles W. Plows
Howard L. Lang
Roger K. Howe
Malcolm S. M. Watts



Second class postage paid at San Francisco and at additional mailing offices (USPS 084 480).

# ANNOUNCING AUDIO-DIGEST

*Totaliy Integrated Medical Education*

## GASTROENTEROLOGY

***Audio-Digest is pleased to announce its newest "Spoken Medical Journal" subscription service.***

***As a charter member you receive:***

- ***CURRENT CLINICAL INFORMATION.*** *Updates, in-depth reviews, and all the latest Gastroenterology information on current developments months ahead of printed publication.*
- ***EDITORIAL EXCELLENCE.*** *Each program is meticulously edited from recordings of meetings and symposia, in all parts of the world, presenting smooth, clear and concise delivery of clinical information.*
- ***ACCOMPANYING PRINTED MATERIALS.*** *Each program includes printed program outline, graphs and charts, references and self-assessment/accreditation examination.*
- ***CATEGORY I APPROVED.*** *Each one-hour program is eligible for two Category I credit hours toward the American Medical Association's Physician's Recognition Award —at no added charge.*
- ***CASSETTE REFERENCE LIBRARY.*** *One full hour program each month in labeled box, with printed syllabus, (plus an annual index useful in locating speaker, topic, or program).*
- ***TAX DEDUCTIBLE.*** *Audio-Digest qualifies as a tax deductible business expense.*
- ***LOW PRICED CHARTER SUBSCRIPTION.*** *Enter your subscription now, and assure yourself of not only receiving Volume I, Issue 1, but you'll also receive two months (two issues) FREE. That's 14 issues (14 months) for the price of 12, for ONLY $69.00—a $50.70 savings off the individual issue price.*

FOR 35 YEARS, THE WORLD'S LEADER IN CONTINUING MEDICAL EDUCATION

## ORDER CERTIFICATE

*YES! I want to become a charter subscriber to Audio-Digest GASTROENTEROLOGY. Please enter my beginning subscription (14 issues for the price of 12)—$69.00. I understand each program includes valuable reference materials and a self-assessment/accreditation test. Pay now and receive a FREE Audio-Digest notebook to house the printed reference materials.*

☐ *Enclosed is my check for $69.00, payable to Audio-Digest Foundation*
☐ *Please bill me for $69.00.*

*FOR FASTER SERVICE CALL: 1-800/423-2308, in California 1-800/232-2165*

*Please print name* _____

*Address* _____

*City* _____ *State* _____ *Zip* _____

( ) _____
*Telephone* *(In case we have a question about your subscription.)*

**Audio-Digest** Foundation®
*A Non-Profit Subsidiary of the California Medical Association*
*1577 East Chevy Chase Drive, Glendale, California 91206*

6663

AIM HIGH

# A PRESCRIPTION FOR PHYSICIANS

**BOTHERED BY:**

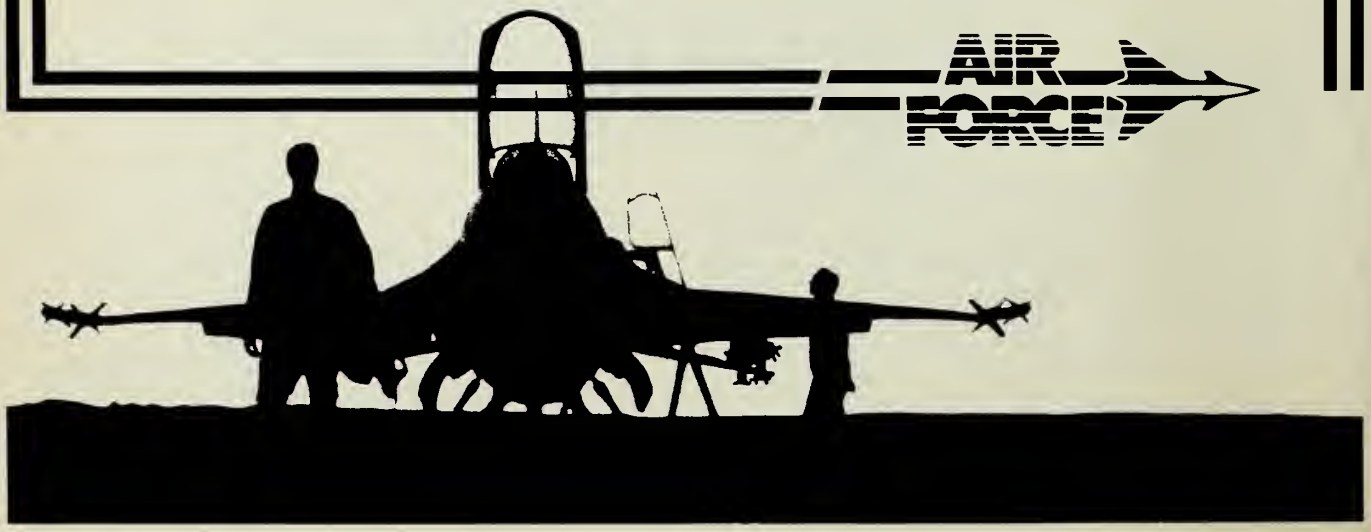
★ Too much paperwork?
★ The burden of office overhead?
★ Malpractice insurance costs?
★ Not enough time for the family?
★ No time to keep current with technology and new methods?
★ No time or money for professional development?

**JOIN THE AIR FORCE MEDICAL TEAM; WE'LL PROVIDE THE FOLLOWING:**

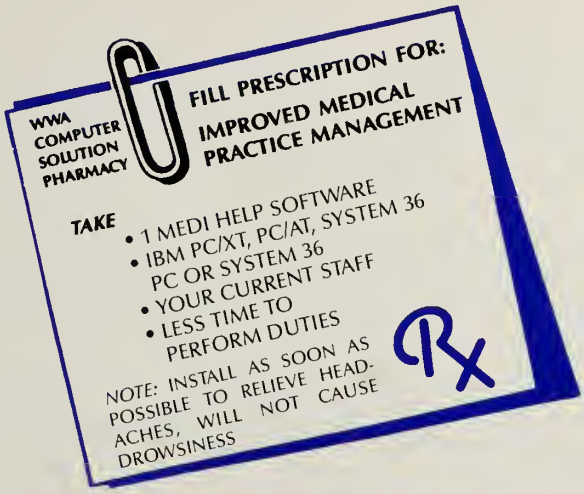
★ Competent and dedicated professional staff.
★ Time for patients and for keeping professionally current.
★ Financial security, a generous retirement for those who qualify.
★ If qualified, unlimited professional development.
★ Medical facilities all around the world.
★ 30 days of vacation with pay each year.
★ Complete medical and dental care.
★ Low cost life insurance.

Want to find out more? Contact your nearest Air Force recruiter for information at no obligation. Call **(801) 582-0276 collect.**

AIR FORCE



# JUST WHAT THE DOCTOR ORDERED




## MEDI HELP AND IBM FOR THE MEDICAL ENVIRONMENT

### FLEXIBILITY

* MEDI HELP will accommodate multiple locations.
* MEDI HELP will handle multiple doctors.
* MEDI HELP will track up to fifteen financial categories with six categories per patient and four insurance carriers per category.
* MEDI HELP will provide insurance billings.
* MEDI HELP will grow with your practice and data can transfer to a larger computer without a conversion.

### CONTROLS

* MEDI HELP will accommodate many terminals and printers, A TRUE MULTI-USER, MULTI-TASKING SYSTEM.
* MEDI HELP provides multi-level security for your practice.
* MEDI HELP provides adjustment reports by operator and choices for posting payments.

### TIME SAVINGS

* MEDI HELP provides addition of new codes for files without terminating the current task.
* MEDI HELP provides HELP KEY SUPPORT.
* MEDI HELP provides default values to reduce keying.
* MEDI HELP provides electronic claims processing.

### EFFICIENCY

* MEDI HELP will locate the patient within files by name search.
* MEDI HELP allows front office super-bills and/or back office operation.
* MEDI HELP provides patient recall notices.

### OUR SERVICES BEGIN WITH YOUR PHONE CALL

* * * Consultation and Needs Analysis
* * * Demonstration at Your Location or Ours
* * * System Installation and Operation Training
* * * Thirty (30) Day Software Trial Period
* * * Local Support in Some Areas
* * * Telephone Support
* * * Periodic Revisions/Enhancements to Software
* * * Assistance with Data Conversion Available
* * * Software Customizing Available

WILLIAMS, WRIGHT & ASSOCIATES, INC.

SINCE 1977

CORPORATE OFFICES
400 N. Mountain Avenue, Suite 305
Upland, California 91786
**(714) 985-0809**

Branch offices located in San Francisco, California and Kennewick, Washington.

MEDICAL PRACTICE MANAGEMENT SYSTEM

NAME:_____ PRACTICE NAME:_____

ADDRESS:_____

CITY:_____ STATE:_____ ZIP:_____

PHONE:_____

MAIL THIS FORM TODAY FOR A HANDS-ON DEMONSTRATION OR A NO COST OR OBLIGATION CONSULTATION.

*An IBM Marketing Assistance Program Participant.* *IBM is a registered trade mark of International Business Machines

For California, Idaho, Montana, Oregon and Washington doctors only.

# The Only Microencapsulated KCl Delivery System That Delivers Both 8mEq K & 10mEq K

## MICRO·K®
(Potassium Chloride)
*Controlled-Release Extencaps® 600 mg (8 mEq K)*

## MICRO·K® 10
(Potassium Chloride)
*Controlled-Release Extencaps® 750 mg (10 mEq K)*

A·H·ROBINS

Pharmaceutical Division, Richmond, Virginia 23261-6609
Member of Certified Medical Representatives Institute

©A.H. Robins Company 1986

The Western Journal of Medicine

VOLUME 146 • NUMBER 4 • APRIL 1987

# CONTENTS


## CLINICAL INVESTIGATION

431 **Blue-Yellow Vision Deficits in Patients With Diabetes**
MELISSA ROCKETT, MSN; DOROTHY ANDERLE, MSN, and ALICE N. BESSMAN, MD
*From the Division of Diabetes, Department of Health Sciences, Rancho Los Amigos Medical Center, Downey, California, and the Department of Medicine, University of Southern California School of Medicine, Los Angeles.*

## CLINICAL MEDICINE

434 **Evaluation and Treatment of Smell Dysfunction**
TERENCE M. DAVIDSON, MD; ALFREDO JALOWAYSKI, PhD; CLAIRE MURPHY, PhD, and ROBERT D. JACOBS, MD
*From the Nasal Dysfunction Clinic; the Division of Head and Neck Surgery, the Department of Surgery; the Pediatric Respiratory and Infectious Diseases Unit, the Department of Pediatrics, and the Department of Continuing Education, University of California, San Diego, Medical Center; the Department of Continuing Education, Veterans Administration Medical Center, and the Department of Psychology, San Diego State University, San Diego.*

439 **Absence of HIV Antibody Among Dental Professionals Exposed to Infected Patients**
NEIL M. FLYNN, MD; STEPHEN M. POLLET, MD; JAMES R. VAN HORNE; RANVEIG ELVEBAKK, MD; SCOTT D. HARPER, and JAMES R. CARLSON, PhD
*From the Division of General Medicine, Departments of Internal Medicine and Pathology, University of California, Davis, School of Medicine.*

## CLINICAL REVIEW

443 **Laboratory Evaluation of Anemia**
RALPH O. WALLERSTEIN, Jr, MD
*From the Departments of Medicine and Laboratory Medicine, University of California, San Francisco, School of Medicine.*

## MEDICAL PROGRESS

452 **Clinical Evaluation and Management of Transient Ischemic Attacks**
JOHN F. ROTHROCK, MD
*From the Division of Neurology, Department of Neurosciences, University of California, San Diego, Medical Center.*

## MEDICAL STAFF CONFERENCE

461 **Current Concepts in the Treatment of Tuberculosis**
Discussant: IRA B. TAGER, MD, MPH
*A discussion selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco, School of Medicine. Taken from a transcription, it was prepared by Drs Homer A. Boushey, Associate Professor of Medicine, and David G. Warnock, Associate Professor of Medicine, under the direction of Dr Lloyd H. Smith, Jr, Professor of Medicine and Associate Dean in the School of Medicine.*

## EPITOMES—IMPORTANT ADVANCES IN CLINICAL MEDICINE

### Orthopedics

*Items of progress in orthopedics. Each item in the judgment of a panel of knowledgeable physicians has recently become reasonably firmly established, both as to scientific fact and important clinical significance.*

466 **Shoulder Arthroscopy**
WESLEY M. NOTTAGE, MD

466 **Microvascular Transfer of Bone—An Update**
GARY K. FRYKMAN, MD

467 **Immediate Stabilization of Fractures in Patients With Multiple-Systems Injuries**
M. W. CHAPMAN, MD

467 **Recent Advances in the Treatment of Chronic Posttraumatic Osteomyelitis of the Tibia**
M. J. PATZAKIS, MD; J. WILKINS, MD, and R. SHERMAN, MD

467 **Biopsy of Primary Bone Tumors**
TILLMAN MOORE, MD

468 **Alternatives to Cemented Joint Prostheses**
RICHARD B. WELCH, MD

468 **Orthopedic and Soft Tissue Applications of Magnetic Resonance Imaging**
DAVID J. SARTORIS, MD, and DONALD RESNICK, MD


*(Continued on Page 409)*

*In mild-to-moderate hypertension†*

# *CAPOTEN (captopril tablets)*

# *THERE'S SAFETY IN OUR NUMBERS*

**• 8 years in clinical use**
CAPOTEN has an established record of practical clinical usage, spanning nearly a decade.

**• 16 million prescriptions**
Since its successful introduction in the U.S., CAPOTEN has earned the prescribing confidence of physicians.[†]

**• 5 million patients**
CAPOTEN has provided well-tolerated therapy for over 5 million patients worldwide.

**• 3,000 clinical papers**
More than 3,000 informative articles have been published about CAPOTEN.

## Convenient, well-tolerated therapy that promotes patient compliance

Comparison of Adverse Effects for CAPOTEN (≤ 100 mg) versus Placebo in Hypertensive Patients with Normal Renal Function (N = 1,622)[‡]

| ADVERSE EFFECT | CAPOTEN (N=1,174) (% affected) | Placebo (N=448) (% affected) |
|---|---|---|
| Headache | 5.2 | 6.9 |
| Rash | 3.7 | 2.5 |
| Dizziness | 3.5 | 2.0 |
| Nausea | 3.2 | 2.0 |
| Fatigue | 3.1 | 2.0 |
| Taste alteration | 1.5 | 1.1 |
| Gastrointestinal | 1.4 | 0.7 |
| Diarrhea | 1.1 | 1.1 |

[‡]None of the differences between captopril and placebo was statistically significant. For the most part, adverse effects were mild and transient and usually did not require discontinuation of therapy. Only 5.5% of the patients in this data base discontinued because of an adverse effect. Data include adverse effects for CAPOTEN with an incidence greater than 1%.

[†]CAPOTEN may be used as initial therapy only for patients with normal renal function in whom the risk of neutropenia/agranulocytosis is relatively low (1 out of over 8,600 in clinical trials). Use special precautions in patients with impaired renal function, collagen vascular disorders, or those exposed to other drugs known to affect the white cells or immune response. Evaluation of hypertensives should always include assessment of renal function. See INDICATIONS AND USAGE, WARNINGS, and ADVERSE REACTIONS in the brief summary on the adjacent page.

ACE*INHIBITOR

**CAPOTEN® captopril tablets** **LOW DOSE**

*FIRST-LINE THERAPY THAT PUTS QUALITY OF LIFE FIRST*

*Angiotensin Converting Enzyme

SQUIBB

**CAPOTEN® TABLETS**
**Captopril Tablets**

**INDICATIONS: Hypertension** – CAPOTEN (captopril) is indicated for the treatment of hypertension. Consideration should be given to the risk of neutropenia/agranulocytosis (see WARNINGS). CAPOTEN may be used as initial therapy for patients with normal renal function, in whom the risk is relatively low. In patients with impaired renal function, particularly those with collagen vascular disease, captopril should be reserved for those who have either developed unacceptable side effects on other drugs, or have failed to respond satisfactorily to drug combinations. CAPOTEN is effective alone and in combination with other antihypertensive agents, especially thiazide-type diuretics.

**Heart Failure:** CAPOTEN (captopril) is indicated in patients with heart failure who have not responded adequately to or cannot be controlled by conventional diuretic and digitalis therapy. CAPOTEN is to be used with diuretics and digitalis.

**WARNINGS: Neutropenia/Agranulocytosis** – Neutropenia ($< 1000/mm^3$) with myeloid hypoplasia has resulted from use of captopril. About half of the neutropenic patients developed systemic or oral cavity infections or other features of the syndrome of agranulocytosis. The risk of neutropenia is dependent on the clinical status of the patient:

In clinical trials in patients with hypertension who have normal renal function (serum creatinine < 1.6 mg/dL and no collagen vascular disease), neutropenia has been seen in one patient out of over 8,600 exposed. In patients with some degree of renal failure (serum creatinine at least 1.6 mg/dL) but no collagen vascular disease, the risk in clinical trials was about 1 per 500. Doses were relatively high in these patients, particularly in view of their diminished renal function. In patients with collagen vascular diseases (e.g., systemic lupus erythematosus, scleroderma) and impaired renal function, neutropenia occurred in 3.7% of patients in clinical trials. While none of the over 750 patients in formal clinical trials of heart failure developed neutropenia, it has occurred during subsequent clinical experience. Of reported cases, about half had serum creatinine ≥ 1.6 mg/dL and more than 75% received procainamide. In heart failure, it appears that the same risk factors for neutropenia are present.

Neutropenia has appeared usually within 3 months after starting therapy, associated with myeloid hypoplasia and frequently accompanied by erythroid hypoplasia and decreased numbers of megakaryocytes (e.g., hypoplastic bone marrow and pancytopenia); anemia and thrombocytopenia were sometimes seen. Neutrophils generally returned to normal in about 2 weeks after captopril was discontinued, and serious infections were limited to clinically complex patients. About 13% of the cases of neutropenia have ended fatally, but almost all fatalities were in patients with serious illness, having collagen vascular disease, renal failure, heart failure or immunosuppressant therapy, or a combination of these complicating factors.

**Evaluation of the hypertensive or heart failure patient should always include assessment of renal function.** If captopril is used in patients with impaired renal function, white blood cell and differential counts should be evaluated prior to starting treatment and at approximately 2-week intervals for about 3 months, then periodically. In patients with collagen vascular disease or who are exposed to other drugs known to affect the white cells or immune response, particularly when there is impaired renal function, captopril should be used only after an assessment of benefit and risk, and then with caution. All patients treated with captopril should be told to report any signs of infection (e.g., sore throat, fever); if infection is suspected, perform counts without delay. Since discontinuation of captopril and other drugs has generally led to prompt return of the white count to normal, upon confirmation of neutropenia (neutrophil count $< 1000/mm^3$) withdraw captopril and closely follow the patient's course.

**Proteinuria** – Total urinary proteins >1 g/day were seen in about 0.7% of patients on captopril. About 90% of affected patients had evidence of prior renal disease or received high doses (>150 mg/day), or both. The nephrotic syndrome occurred in about one-fifth of proteinuric patients. In most cases, proteinuria subsided or cleared within 6 months whether or not captopril was continued. The BUN and creatinine were seldom altered in proteinuric patients. Since most cases of proteinuria occurred by the 8th month of therapy, patients with prior renal disease or those receiving captopril at doses >150 mg/day should have urinary protein estimates (dip-stick on 1st morning urine) before therapy, and periodically thereafter.

**Hypotension** – Excessive hypotension was rarely seen in hypertensive patients but is a possibility in severely salt/volume-depleted persons such as those treated vigorously with diuretics (see PRECAUTIONS [Drug Interactions]).

In heart failure, where blood pressure was either normal or low, transient decreases in mean blood pressure >20% were recorded in about half of the patients. This transient hypotension may occur after any of the first several doses and is usually well tolerated, although rarely it has been associated with arrhythmia or conduction defects. A starting dose of 6.25 or 12.5 mg tid may minimize the hypotensive effect. Patients should be followed closely for the first 2 weeks of treatment and whenever the dose of captopril and/or diuretic is increased.

**BECAUSE OF THE POTENTIAL FALL IN BLOOD PRESSURE IN THESE PATIENTS, THERAPY SHOULD BE STARTED UNDER VERY CLOSE MEDICAL SUPERVISION.**

**PRECAUTIONS: General:** *Impaired Renal Function,* Hypertension – Some hypertensive patients with renal disease, particularly those with severe renal artery stenosis, have developed increases in BUN and serum creatinine. It may be necessary to reduce captopril dosage and/or discontinue diuretic. For some of these patients, normalization of blood pressure and maintenance of adequate renal perfusion may not be possible. Heart Failure – About 20% of patients develop stable elevations of BUN and serum creatinine >20% above normal or baseline upon long-term treatment. Less than 5% of patients, generally with severe preexisting renal disease, required discontinuation due to progressively increasing creatinine. See DOSAGE AND ADMINISTRATION, ADVERSE REACTIONS [Altered Laboratory Findings]. *Valvular Stenosis* – A theoretical concern, for risk of decreased coronary perfusion, has been noted regarding vasodilator treatment in patients with aortic stenosis due to decreased afterload reduction.

*Surgery/Anesthesia* – If hypotension occurs during major surgery or anesthesia, and is considered due to the effects of captopril, it is correctable by volume expansion.

**Drug Interactions:** *Hypotension: Patients on Diuretic Therapy* – Precipitous reduction of blood pressure may occasionally occur within the 1st hour after administration of the initial captopril dose in patients on diuretics, especially those recently placed on diuretics, and those on severe dietary salt restriction or dialysis. This possibility can be minimized by either discontinuing the diuretic or increasing the salt intake about 1 week prior to initiation of captopril therapy or by initiating therapy with small doses (6.25 or 12.5 mg). Alternatively, provide medical supervision for at least 1 hour after the initial dose.

*Agents Having Vasodilator Activity* – In heart failure patients, vasodilators should be administered with caution.

*Agents Causing Renin Release* – Captopril's effect will be augmented by antihypertensive agents that cause renin release.

*Agents Affecting Sympathetic Activity* – The sympathetic nervous system may be especially important in supporting blood pressure in patients receiving captopril alone or with diuretics. Beta-adrenergic blocking drugs add some further antihypertensive effect to captopril, but the overall response is less than additive. Therefore, use agents affecting sympathetic activity (e.g., ganglionic blocking agents or adrenergic neuron blocking agents) with caution.

*Agents Increasing Serum Potassium* – Give potassium-sparing diuretics or potassium supplements only for documented hypokalemia, and then with caution, since they may lead to a significant increase of serum potassium. Use potassium-containing salt substitutes with caution.

*Inhibitors of Endogenous Prostaglandin Synthesis* – Indomethacin and other nonsteroidal anti-inflammatory agents may reduce the antihypertensive effect of captopril, especially in low renin hypertension.

**Drug/Laboratory Test Interaction:** Captopril may cause a false-positive urine test for acetone.

**Carcinogenesis, Mutagenesis and Impairment of Fertility:** Two-year studies with doses of 50 to 1350 mg/kg/day in mice and rats failed to show any evidence of carcinogenic potential. Studies in rats have revealed no impairment of fertility.

**Pregnancy: Category C** – There are no adequate and well-controlled studies in pregnant women. Embryocidal effects and craniofacial malformations were observed in rabbits. Therefore, captopril should be used during pregnancy, or for patients likely to become pregnant, only if the potential benefit outweighs the potential risk to the fetus. Captopril crosses the human placenta.

**Nursing Mothers:** Captopril is secreted in human milk. Exercise caution when administering captopril to a nursing woman, and, in general, nursing should be interrupted.

**Pediatric Use:** Safety and effectiveness in children have not been established although there is limited experience with use of captopril in children from 2 months to 15 years of age. Dosage, on a weight basis, was comparable to that used in adults. Captopril should be used in children only if other measures for controlling blood pressure have not been effective.

**ADVERSE REACTIONS:** Reported incidences are based on clinical trials involving approximately 7000 patients.

*Renal* – About 1 of 100 patients developed proteinuria (see WARNINGS). Renal insufficiency, renal failure, polyuria, oliguria, and urinary frequency in 1 to 2 of 1000 patients.

*Hematologic* – Neutropenia/agranulocytosis have occurred (see WARNINGS). Anemia, thrombocytopenia, and pancytopenia have been reported.

*Dermatologic* – Rash (usually maculopapular, rarely urticarial), often with pruritus and sometimes with fever and eosinophilia, in about 4 to 7 of 100 patients (depending on renal status and dose), usually during the 1st 4 weeks of therapy. Pruritus, without rash, in about 2 of 100 patients. A reversible associated pemphigoid-like lesion, and photosensitivity have also been reported. Angioedema of the face, mucous membranes of the mouth, or of the extremities in about 1 of 1000 patients – reversible on discontinuance of captopril therapy. One case of laryngeal edema reported. Flushing or pallor in 2 to 5 of 1000 patients.

*Cardiovascular* – Hypotension may occur, see WARNINGS and PRECAUTIONS (Drug Interactions) for discussion of hypotension on initiation of captopril therapy. Tachycardia, chest pain, and palpitations each in about 1 of 100 patients. Angina pectoris, myocardial infarction, Raynaud's syndrome, and congestive heart failure each in 2 to 3 of 1000 patients.

*Dysgeusia* – About 2 to 4 (depending on renal status and dose) of 100 patients developed a diminution or loss of taste perception; taste impairment is reversible and usually self-limited even with continued drug use (2 to 3 months). Gastric irritation, abdominal pain, nausea, vomiting, diarrhea, anorexia, constipation, aphthous ulcers, peptic ulcer, dizziness, headache, malaise, fatigue, insomnia, dry mouth, dyspnea, cough, alopecia, and paresthesias reported in about 0.5 to 2% of patients but did not appear at increased frequency compared to placebo or other treatments used in controlled trials.

**Altered Laboratory Findings:** Elevations of liver enzymes in a few patients although no causal relationship has been established. Rarely cholestatic jaundice and hepatocellular injury with or without secondary cholestasis, have been reported. A transient elevation of BUN and serum creatinine may occur, especially in volume-depleted or renovascular hypertensive patients. In instances of rapid reduction of longstanding or severely elevated blood pressure, the glomerular filtration rate may decrease transiently, also resulting in transient rises in serum creatinine and BUN. Small increases in serum potassium concentration frequently occur, especially in patients with renal impairment (see PRECAUTIONS).

**OVERDOSAGE:** Primary concern is correction of hypotension. Volume expansion with an I.V. infusion of normal saline is the treatment of choice for restoration of blood pressure. Captopril may be removed from the general circulation by hemodialysis.

**DOSAGE AND ADMINISTRATION:** CAPOTEN (captopril) should be taken one hour before meals. In hypertension, CAPOTEN may be dosed bid or tid. Dosage must be individualized; see DOSAGE AND ADMINISTRATION section of package insert for detailed information regarding dosage in hypertension and in heart failure. Because CAPOTEN (captopril) is excreted primarily by the kidneys, dosage adjustments are recommended for patients with impaired renal function.

**Consult package insert before prescribing CAPOTEN (captopril).**

**HOW SUPPLIED:** Available in tablets of 12.5, 25, 50, and 100 mg in bottles of 100 (25 mg also available in bottles of 1000), and in UNIMATIC® single dose packs of 100 tablets. (J3-658D)

References:
1. PDS Alpha, *National Prescription Report,* Pharmaceutical Data Services, Subsidiary of McKesson Corporation.
2. Data on file, Squibb Institute for Medical Research.

SQUIBB

*INNOVATORS IN CARDIOVASCULAR MEDICINE*

©1987 E. R. Squibb & Sons, Inc., Princeton, NJ 527-555 Issued: January 1987

(Continued from Page 405)

469 **Meniscal Repair**
THOMAS D. ROSENBERG, MD; LONNIE E. PAULOS, MD, and RICHARD D. PARKER, MD

469 **Sports Footwear**
RICHARD A. MARDER, MD

469 **Osseous and Osteochondral Allografts**
MARVIN H. MEYERS, MD

470 **Endoprosthetic Limb Salvage Operation for Malignant Bone Tumors**
JEFFREY J. ECKARDT, MD

## EDITORIALS

471 **Health Care in a Dreamworld**

471 **Diagnosis and Treatment of Smell and Taste Disorders**
SUSAN S. SCHIFFMAN, PhD
*Dr Schiffman is Professor of Medical Psychology, Department of Psychiatry, Duke Medical Center, Durham, North Carolina.*

473 **Clinical Evaluation of Anemia**
HELEN M. RANNEY, MD
*Dr Ranney is Professor of Medicine, Department of Medicine, University of California, San Diego, School of Medicine, La Jolla.*

474 **Transient Ischemic Attacks**
J. DONALD EASTON, MD
*Dr Easton is Professor and Chair, Program in Neurology, Department of Neurology, Rhode Island Hospital-Brown University, Providence, Rhode Island.*

475 **It Can Be a Lethal Instrument**

## CASE REPORTS

476 **Myasthenia Gravis and Hyperthyrotropinemia in a Child**
SUSAN M. SCOTT, MD; ALAN H. KLEIN, MD, and JO ANNE BRASEL, MD
*From the Department of Pediatrics, University of New Mexico School of Medicine, Albuquerque; the Department of Pediatrics, Cedars-Sinai Medical Center, Los Angeles, and the Department of Pediatrics, Harbor-UCLA Medical Center, Torrance, California.*

479 ***Streptococcus sanguis II* (Viridans) Prosthetic Valve Endocarditis With Myocardial, Splenic and Cerebral Abscesses**
STEPHEN G. YOUNG, MD; THOMAS DAVEE, MD; JOSHUA FIERER, MD, and MITCH K. MOREY, MD
*From the Cardiology Division, Veterans Administration Medical Center, San Diego, and the Department of Medicine, University of California, San Diego, School of Medicine. Dr Young is now with the Gladstone Foundation Laboratory, San Francisco.*

481 **Sarcoidosis Presenting as Chronic Thrombocytopenia**
STEPHEN K. FIELD, MD, FRCP(C), and MAN-CHIU POON, MD
*From the Pulmonary and Hematology Divisions, Department of Medicine, Foothills Provincial Hospital, University of Calgary Faculty of Medicine, Calgary.*

482 **Atypical Diffuse Angiosarcoma of the Liver**
GARY C. KANEL, MD; JACOB KORULA, MD; CHOONG T. LIEW, MD, and ROBERT L. PETERS, MD
*From the University of Southern California Liver Unit, Department of Pathology, Rancho Los Amigos Medical Center, Downey, California, and the Departments of Clinical Pathology and Clinical Medicine, University of Southern California School of Medicine, Los Angeles.*

## CORRESPONDENCE

486 **Addendum to Living Will**
W. A. REYNOLDS, MD

486 **Cost-Effectiveness of Fecal Occult Blood Screening**
THEODORE G. GANIATS, MD, and WILLIAM A. NORCROSS, MD

487 **Was It Worth It?**
RICHARD M. COHEN, MD
GLENN W. DRUMHELLER, DO

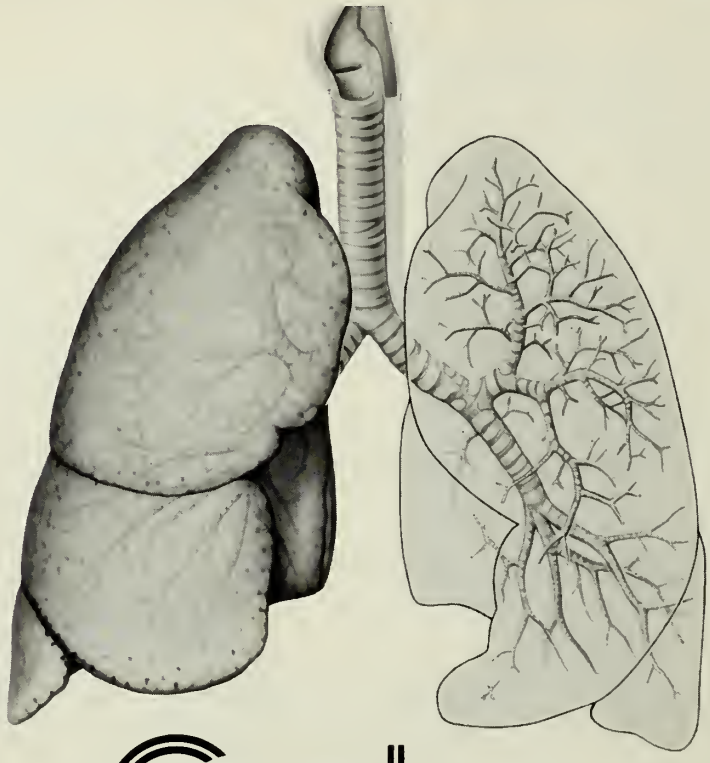
487 **Natural Death Acts**
WILLIAM O. ROBERTSON, MD

488 **Cognitive-Procedural Differences**
PHILIP R. ALPER, MD

488 **Illness From Organophosphate Exposure**
ANTONIO R. VELASCO, MD; PAUL G. BARNETT, and JOHN E. MIDTLING, MD, MS

(Continued on Page 416)

# Consider the causative organisms...



# Ceclor®
## cefaclor

## 250-mg Pulvules® t.i.d. offers effectiveness against the major causes of bacterial bronchitis

***Haemophilus influenzae*, *H influenzae*, *Streptococcus pneumoniae*, *Streptococcus pyogenes***
(ampicillin-susceptible) (ampicillin-resistant)

*Note:* Ceclor® is contraindicated in patients with known allergy to the cephalosporins and should be given cautiously to penicillin-allergic patients.

Penicillin is the usual drug of choice in the treatment and prevention of streptococcal infections, including the prophylaxis of rheumatic fever. See prescribing information.

**Ceclor®** (cefaclor)

**Summary. Consult the package literature for prescribing information.**

**Indications:** Lower respiratory infections, including pneumonia, caused by susceptible strains of *Streptococcus pneumoniae, Haemophilus influenzae,* and *S. pyogenes* (group A beta-hemolytic streptococci).

**Contraindications:** Known allergy to cephalosporins.

**Warnings:** CECLOR SHOULD BE ADMINISTERED CAUTIOUSLY TO PENICILLIN-SENSITIVE PATIENTS. PENICILLINS AND CEPHALOSPORINS SHOW PARTIAL CROSS-ALLERGENICITY. POSSIBLE REACTIONS INCLUDE ANAPHYLAXIS.

Administer cautiously to allergic patients.

Pseudomembranous colitis has been reported with virtually all broad-spectrum antibiotics. It must be considered in differential diagnosis of antibiotic-associated diarrhea. Colon flora is altered by broad-spectrum antibiotic treatment, possibly resulting in antibiotic-associated colitis.

**Precautions:**

- Discontinue Ceclor in the event of allergic reactions to it.
- Prolonged use may result in overgrowth of nonsusceptible organisms.
- Positive direct Coombs' tests have been reported during treatment with cephalosporins.
- In renal impairment, safe dosage of Ceclor may be lower than that usually recommended. Ceclor should be administered with caution in such patients.
- Broad-spectrum antibiotics should be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis.
- Safety and effectiveness have not been determined in pregnancy, lactation, and infants less than one month old. Ceclor penetrates mother's milk. Exercise caution in prescribing for these patients.

**Adverse Reactions:** (percentage of patients)

Therapy-related adverse reactions are uncommon. Those reported include:

- Gastrointestinal (mostly diarrhea): 2.5%.
- Symptoms of pseudomembranous colitis may appear either during or after antibiotic treatment.
- Hypersensitivity reactions (including morbilliform eruptions, pruritus, urticaria, erythema multiforme, serum-sickness-like reactions): 1.5%; usually subside within a few days after cessation of therapy. These reactions have been reported more frequently in children than in adults and have usually occurred during or following a second course of therapy with Ceclor. No serious sequelae have been reported. Antihistamines and corticosteroids appear to enhance resolution of the syndrome.
- Cases of anaphylaxis have been reported, half of which have occurred in patients with a history of penicillin allergy.
- Other: eosinophilia, 2%; genital pruritus or vaginitis, less than 1%.

**Abnormalities in laboratory results of uncertain etiology**

- Slight elevations in hepatic enzymes.
- Transient fluctuations in leukocyte count (especially in infants and children)
- Abnormal urinalysis; elevations in BUN or serum creatinine
- Positive direct Coombs' test
- False-positive tests for urinary glucose with Benedict's or Fehling's solution and Clinitest® tablets but not with Tes-Tape® (glucose enzymatic test strip, Lilly)

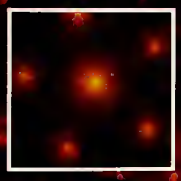
© 1986, ELI LILLY AND COMPANY [060485LR]

*Additional information available to the profession on request from Eli Lilly and Company, Indianapolis, Indiana 46285.*

Eli Lilly Industries, Inc.
Carolina, Puerto Rico 00630
600332

# *Advantages beyond control...*

# For the hypertensive patient:



## Proven long-term blood pressure control

In a 2-year study, CORGARD® (nadolol tablets) effectively controlled blood pressure in 164 hypertensive patients with no apparent loss of efficacy.[1]

## Good CNS side effect profile

Since CORGARD is highly hydrophilic, CNS side effects are rarely a problem.*

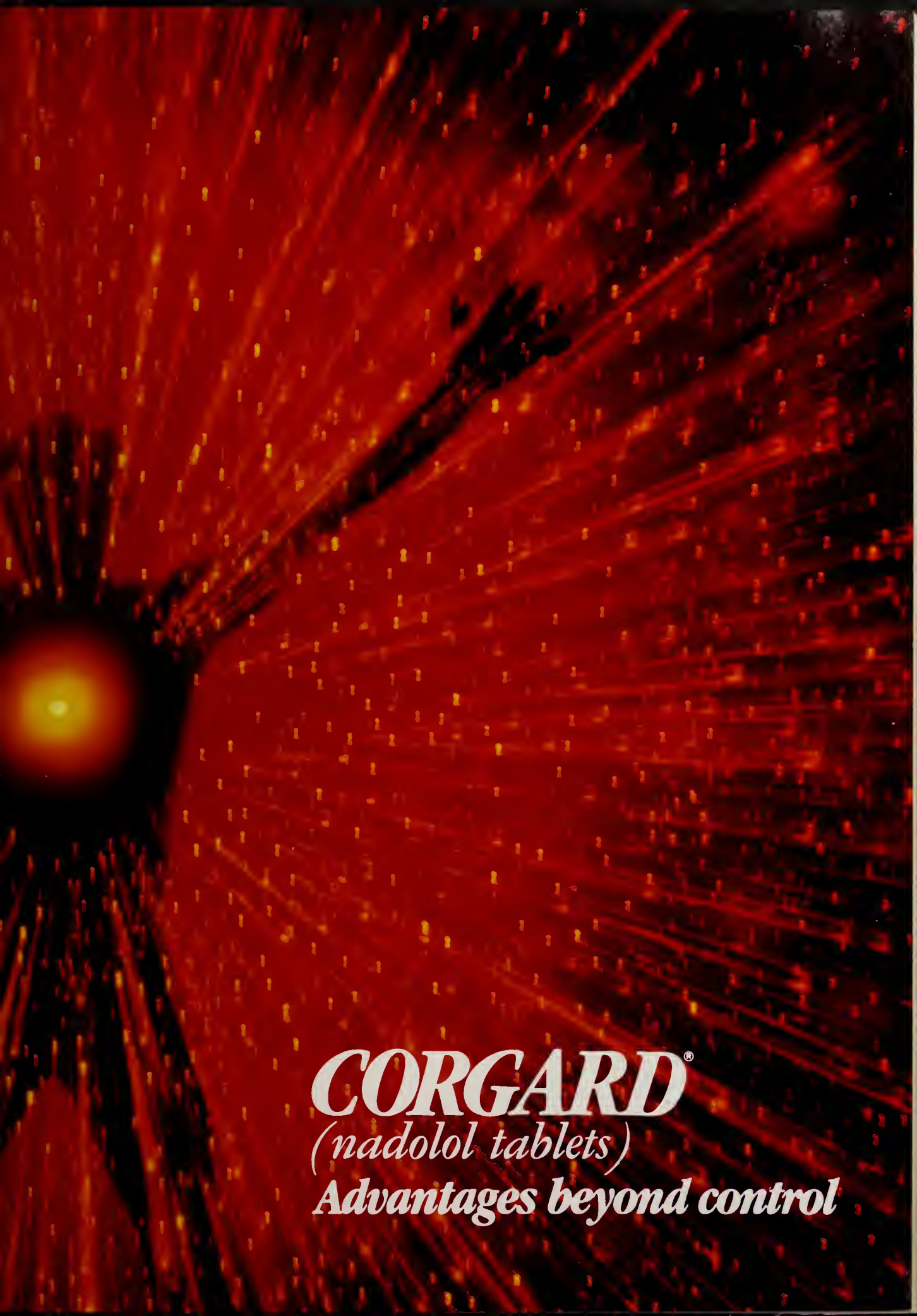
## Preserves renal blood flow

Reduced renal blood flow may exacerbate hypertension. CORGARD controls blood pressure and preserves renal blood flow.

## Once-a-day convenience

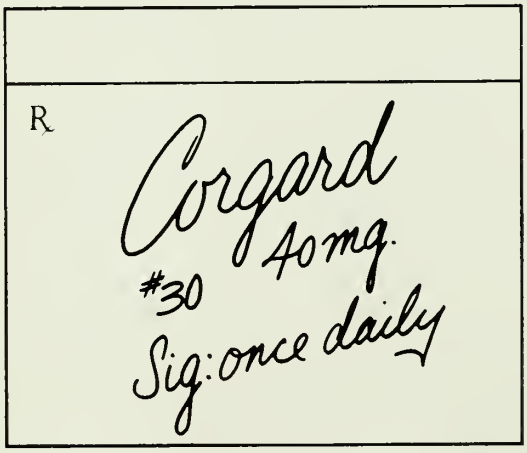
CORGARD once a day simplifies the dosage regimen and helps enhance patient compliance.

***For a complete discussion of CONTRAINDICATIONS, PRECAUTIONS, ADVERSE REACTIONS, and WARNINGS, including avoidance of abrupt withdrawal, please see the brief summary of prescribing information on the last page of this advertisement.**


CORGARD®
(nadolol tablets)
Advantages beyond control

# CORGARD®
## (nadolol tablets)

## *Advantages beyond control for the hypertensive patient*




**CORGARD® TABLETS**
**Nadolol Tablets**

**DESCRIPTION:** CORGARD (nadolol) is a synthetic non-selective beta-adrenergic receptor blocking agent.

**CONTRAINDICATIONS:** Bronchial asthma, sinus bradycardia and greater than first degree conduction block, cardiogenic shock, and overt cardiac failure (see WARNINGS).

**WARNINGS: Cardiac Failure**—Sympathetic stimulation may be a vital component supporting circulatory function in congestive heart failure, and its inhibition by beta-blockade may precipitate more severe failure. Although beta-blockers should be avoided in overt congestive heart failure, if necessary, they can be used with caution in patients with a history of failure who are well-compensated, usually with digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle. IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta-blockers can, in some cases, lead to cardiac failure; therefore, at first sign or symptom of heart failure, digitalize and/or give diuretics, and closely observe response, or discontinue nadolol (gradually if possible).

**Exacerbation of Ischemic Heart Disease Following Abrupt Withdrawal**—Hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred after *abrupt* discontinuation of such therapy. When discontinuing chronic use of nadolol, particularly in patients with ischemic heart disease, gradually reduce dosage over a 1- to 2- week period and carefully monitor the patient. Reinstitute nadolol promptly (at least temporarily) and take other measures appropriate for management of unstable angina if angina markedly worsens or acute coronary insufficiency develops. Warn patients not to interrupt or discontinue therapy without physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue nadolol therapy abruptly even in patients treated only for hypertension.

**Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema)**—PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA-BLOCKERS. Administer nadolol with caution since it may block bronchodilation produced by endogenous or exogenous catecholamine stimulation of $beta_2$ receptors.

**Major Surgery**—Because beta blockade impairs the ability of the heart to respond to reflex stimuli and may increase risks of general anesthesia and surgical procedures, resulting in protracted hypotension or low cardiac output, it has generally been suggested that such therapy should be withdrawn several days prior to surgery. Recognition of the increased sensitivity to catecholamines of patients recently withdrawn from beta-blocker therapy, however, has made this recommendation controversial. If possible, withdraw beta-blockers well before surgery takes place. In emergency surgery, inform the anesthesiologist that the patient is on beta-blocker therapy. Use of beta-receptor agonists such as isoproterenol, dopamine, dobutamine, or levarterenol can reverse the effects of nadolol. Difficulty in restarting and maintaining the heart beat has also been reported with beta-adrenergic receptor blocking agents.

**Diabetes and Hypoglycemia**—Beta-adrenergic blockade may prevent the appearance of premonitory signs and symptoms (e.g., tachycardia and blood pressure changes) of acute hypoglycemia. This is especially important with labile diabetics. Beta-blockade also reduces release of insulin in response to hyperglycemia; therefore, it may be necessary to adjust dose of antidiabetic drugs.

**Thyrotoxicosis**—Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. To avoid abrupt withdrawal of beta-adrenergic blockade which might precipitate a thyroid storm, carefully manage patients suspected of developing thyrotoxicosis.

**PRECAUTIONS: Impaired Renal Function**—Use nadolol with caution (see DOSAGE AND ADMINISTRATION section of package insert).

**Information for Patients**—Warn patients, especially those with evidence of coronary artery insufficiency, against interruption or discontinuation of nadolol without physician's advice. Although cardiac failure rarely occurs in properly selected patients, advise patients being treated with beta-adrenergic blocking agents to consult physician at first sign of impending failure. Advise patients in event of missed doses.

**Drug Interactions**—Concurrent administration may result in interactions with: Anesthetics, general—exaggeration of the hypotension induced by general anesthetics (see WARNINGS, Major Surgery). Antidiabetic drugs (oral agents and insulin)—hypoglycemia or hyperglycemia; adjust antidiabetic drug dosage accordingly (see WARNINGS, Diabetes and Hypoglycemia). Catecholamine-depleting drugs (e.g., reserpine)—additive effect; monitor closely for hypotension and/or excessive bradycardia.

**Carcinogenesis, Mutagenesis, Impairment of Fertility**—In 1 to 2 years oral toxicology studies in mice, rats, and dogs, nadolol did not produce significant toxic effects. In 2-year oral carcinogenic studies in rats and mice, nadolol did not produce neoplastic, preneoplastic, or nonneoplastic pathologic lesions.

**Pregnancy Category C**—In animal reproduction studies with nadolol, evidence of embryo- and fetotoxicity was found in rabbits (but not in rats or hamsters) at doses 5 to 10 times greater (on a mg/kg basis) than maximum indicated human dose; no teratogenic potential was seen in any of these species. There are no well-controlled studies in pregnant women; therefore, use nadolol in pregnant women only if potential benefit justifies potential risk to the fetus. Neonates of mothers who received nadolol at parturition have exhibited bradycardia, hypoglycemia and associated symptoms.

**Nursing Mothers**—Nadolol is excreted in human milk. Exercise caution when nadolol is administered to a nursing woman.

**Pediatric Use**—Safety and effectiveness in children have not been established.

**ADVERSE REACTIONS:** Most adverse effects have been mild and transient and have rarely required nadolol withdrawal.

**Cardiovascular**—Bradycardia with heart rates of less than 60 beats per minute occurs commonly, and heart rates below 40 beats per minute and/or symptomatic bradycardia were seen in about 2 of 100 patients. Symptoms of peripheral vascular insufficiency, usually of the Raynaud type, have occurred in approximately 2 of 100 patients. Cardiac failure, hypotension, and rhythm/conduction disturbances have each occurred in about 1 of 100 patients. Single instances of first degree and third degree heart block have been reported; intensification of AV block is a known effect of beta-blockers (see also CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS). **Central Nervous System**—Dizziness or fatigue reported in approximately 2 of 100 patients; paresthesias, sedation, and change in behavior reported in approximately 6 of 1000 patients. **Respiratory**—Bronchospasm reported in approximately 1 of 1000 patients (see CONTRAINDICATIONS and WARNINGS). **Gastrointestinal**—Nausea, diarrhea, abdominal discomfort, constipation, vomiting, indigestion, anorexia, bloating, and flatulence each reported in 1 to 5 of 1000 patients. **Miscellaneous**—Each of the following reported in 1 to 5 of 1000 patients: rash; pruritus; headache; dry mouth, eyes, or skin; impotence or decreased libido; facial swelling; weight gain; slurred speech; cough; nasal stuffiness; sweating; tinnitus; blurred vision; infrequent reversible alopecia.

The following adverse reactions have been reported in patients taking nadolol and/or other beta-adrenergic blocking agents, but no causal relationship to nadolol has been established: **Central Nervous System**—reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place; short-term memory loss, emotional lability with slightly clouded sensorium; decreased performance on neuropsychometrics. **Gastrointestinal**—mesenteric arterial thrombosis; ischemic colitis; elevated liver enzymes. **Hematologic**—agranulocytosis; thrombocytopenic or nonthrombocytopenic purpura. **Allergic**— fever combined with aching and sore throat; laryngospasm; respiratory distress. **Miscellaneous**—pemphigoid rash; hypertensive reaction in patients with pheochromocytoma; sleep disturbances; Peyronie's disease. The oculomucocutaneous syndrome associated with practolol has not been reported with nadolol.

**OVERDOSAGE:** Nadolol can be removed from the general circulation by hemodialysis. In addition to gastric lavage, employ the following measures as appropriate. In determining duration of corrective therapy, take note of long duration of effect of nadolol.

**Excessive Bradycardia**—Administer atropine (0.25 to 1.0 mg). If there is no response to vagal blockade, administer isoproterenol cautiously.

**Cardiac Failure**—Administer a digitalis glycoside and diuretic. It has been reported that glucagon may also be useful in this situation.

**Hypotension**—Administer vasopressors, e.g., epinephrine or levarterenol. (There is evidence that epinephrine may be the drug of choice.)

**Bronchospasm**—Administer a $beta_2$-stimulating agent and/or a theophylline derivative.

**DOSAGE**—For all patients, DOSAGE MUST BE INDIVIDUALIZED.

For **angina pectoris,** usual initial dose is 40 mg q.d.; may be gradually increased in 40 to 80 mg increments at 3 to 7 day intervals until optimum clinical response or pronounced slowing of the heart rate; usual maintenance dose is 40 or 80 mg q.d. (doses up to 160 or 240 mg daily may be needed). If treatment is to be discontinued, reduce dosage gradually over a period of 1 to 2 weeks (see WARNINGS).

For **hypertension,** usual initial dose is 40 mg q.d.; gradually increase in 40 to 80 mg increments until optimum blood pressure reduction is achieved; usual maintenance dose is 40 or 80 mg q.d. (doses up to 240 or 320 mg daily may be needed).

Patients with renal failure require adjustment in dosing interval; see package insert for dosage in these patients.

**For full prescribing information consult package insert.**

**HOW SUPPLIED:** In scored tablets containing 40, 80, 120, or 160 mg nadolol per tablet in bottles of 100 and in Unimatic® unit-dose packs of 100 tablets. The 40 mg, 80 mg, and 120 mg potencies are also available in bottles of 1000 tablets. (J3-527E)

**References:** 1. Alexander JC, Christie MH, Vernam KA, et al: Long-term experience with nadolol in treatment of hypertension and angina pectoris. Am Heart J 108:1136-1140, 1984

PRINCETON PHARMACEUTICAL PRODUCTS
A SQUIBB COMPANY

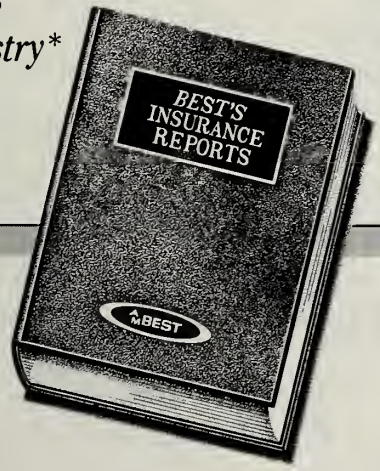
© 1987 E.R. Squibb & Sons, Inc. Princeton, NJ

517-532

Issued January

# Check our vital signs.

*A+ Rating from A.M. Best Company, the Bible of the insurance industry**




More physicians in California depend upon SCPIE than any other company for their professional liability insurance. There are many reasons why SCPIE is the leader. Check them out:

- **Rates:** This is your bottom line. SCPIE rates are highly competitive. "Profits" are returned to the policyholders through Experience Credits.
- **Stability:** SCPIE has a history of stable rates and financial strength. SCPIE has adequate reserves to pay anticipated claims, plus surplus to cover unexpected losses. SCPIE is reinsured with Lloyds of London.
- **Non-assessability:** You cannot be assessed if claims experience turns sour. SCPIE is a top-flight *insurance* company, not a cooperative which requires you to assume unlimited liability for others' losses.
- **Claims Handling:** A claim is a traumatic experience. You get highly qualified legal counsel, experienced in professional liability claims. Three out of four claims are closed without payment. Our record of defense verdicts is over 85%.
- **Underwriting:** Physicians review all applications requesting nose coverage and/or with claims history. SCPIE also maintains an on-going underwriting process to be sure members meet quality standards.
- **Local physician control:** SCPIE is owned by its physician policyholders, who elect physicians to run it. They make sure that overhead is low and performance is high.

** SCPIE is one of only five physician-owned companies in the nation to have the Best's A+ rating. We are the largest of them all.*

**scpie**

Southern California Physicians Insurance Exchange

2029 Century Park East
Suite 2300
Los Angeles, CA 90067
(213) 552-8900

(Continued from Page 409)

488 **Educating the Public About Life-Style and Nutritional Practices**
IRA E. BAILIE, MD

489 **Healing the Healers**
JOHN J. MOHR, MD

489 **Correction: Common AIDS-Related Problems**
NANCY KURAHASHI

TOPICS IN PRIMARY CARE MEDICINE

490 **Screening in Preventive Care for Adolescents**
PAULA BRAVEMAN, MD, and KATHLEEN E. TOOMEY, MD, MPH
*From the Division of Family and Community Medicine and the Institute for Health Policy Studies, University of California, San Francisco, School of Medicine.*

HEALTH CARE DELIVERY

494 **Physicians as Patients—The Use of Obstetric Technology in Physician Families**
CARIN E. DUGOWSON, MD, MPH, and STEPHEN K. HOLLAND, MD
*From the Division of Rheumatology, Department of Medicine, Pacific Medical Center and University of Washington, Seattle, and the Health Data Institute, Lexington, Massachusetts.*

PUBLIC HEALTH AND PREVENTIVE MEDICINE

497 **Injuries and Fatalities Associated With Off-Road Three-Wheeled All-Terrain Vehicles**
C. MACK SEWELL, PhD; JEFFREY S. PINE, MSPH, and HARRY F. HULL, MD
*From the Office of Epidemiology and the Injury Control Program, New Mexico Health and Environment Department, Santa Fe.*

ALTERNATIVE FORMS OF THERAPY

499 **Using Resistant Behaviors in the Treatment of Alcoholic Patients**
LA VERA M. CRAWLEY, MD
*From the Family Practice Residency Program, Division of Family and Community Medicine, San Francisco General Hospital Medical Center and the University of California, San Francisco, School of Medicine. Dr Crawley is now Alcohol Services Coordinator at Inscription House Indian Health Center, Shonto, Arizona.*

IN THE FOREFRONT

502 **Teaching Spanish and Cross-cultural Sensitivity to Medical Students**
TERESA GONZALEZ-LEE, PhD, and HAROLD J. SIMON, MD, PhD
*From the Department of Community and Family Medicine, University of California, San Diego, School of Medicine, La Jolla.*

INFORMATION

505 **Nailing Down the Cause of Periungual Lesions**
HENRY SCHNEIDERMAN, MD, and ANN L. PARKE, MD, FRCP(C)
*From the Divisions of Pathology and Rheumatology, Department of Medicine, University of Connecticut Health Center, Farmington.*

OTHER FEATURES

423 **Books Received**
424 **Western Continuing Medical Education Activities**
433 **Book Review**
451 **Software Review**
498 **Medical Practice Question**
513 **In Memoriam**
525 **Classified Advertising**
529 **Subscription Information**
534 **Western State Medical Associations' Meetings**

★ **Official Journal of the Arizona Medical Association, the California Medical Association, the Idaho Medical Association, the Montana Medical Association, the Nevada State Medical Association, the New Mexico Medical Society, the Utah State Medical Association, the Washington State Medical Association and the Wyoming Medical Society. Affiliated Specialty Society: California Society of Internal Medicine.**

★ **Affiliated Clinical Investigation Societies: the Western Association of Physicians; the Western Society for Clinical Investigation; the Western Section, American Federation for Clinical Research; the Western Society for Pediatric Research; the Western Region, Society for Investigative Dermatology.**

## Technology

THE RESIDENT" is a compre-
ensive medical office computer
ystem designed to meet the
omplex needs of today's
edical office.

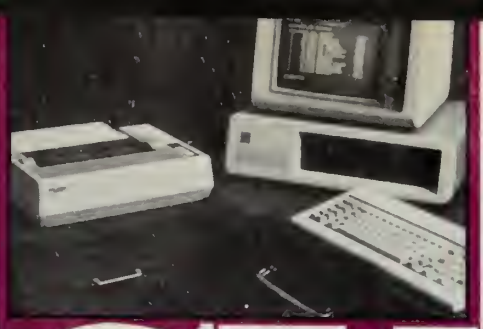
ll programs in "THE RESIDENT"
re accessed through menus.
)perations are smooth and
asy. Patient record access can
e by name, partial name, or
ffice-defined code. Mainten-
nce tables (RVS, ICD-9, Insur-
nce Company, etc.) may be set
p using existing codes com-
non to the particular office.

)perations may be temporarily
uspended, a new task per-
ormed, and then resume the
riginal task at the exact place
vhere operation was sus-
ended. This feature is useful
or adding a new insurance
ompany without having to skip
hrough numerous screens.

his software was designed for
roup practices, but performs
qually as well in a busy solo
ractice.

## Support Service

or over 7 years, SYZYGY has
rovided such services as: com-
uter installations, cabling,
ser training, management con-
ulting, and hardware/software
upport.



# SYZYGY

## Key Features

- *Latest industry-accepted software technology*
- *Protection against software obsolescence*
- *Modular software application packages*
- *Multi-user/multi-terminals/multi-office*
- *Three tiered self-help capability*
- *Office defined practice policies*
- *No codes to remember*
- *Suspend an operation, jump to a new task, and return*
- *Bridge between database and word processor*

## Modular Software

With Wallaby's modular software, there is never a need to purchase and implement more capability than you need. You buy only what you require. Each software configuration, however, is complete of itself...there are no costly options to any module to fill the needs of a particular medical speciality. For example:

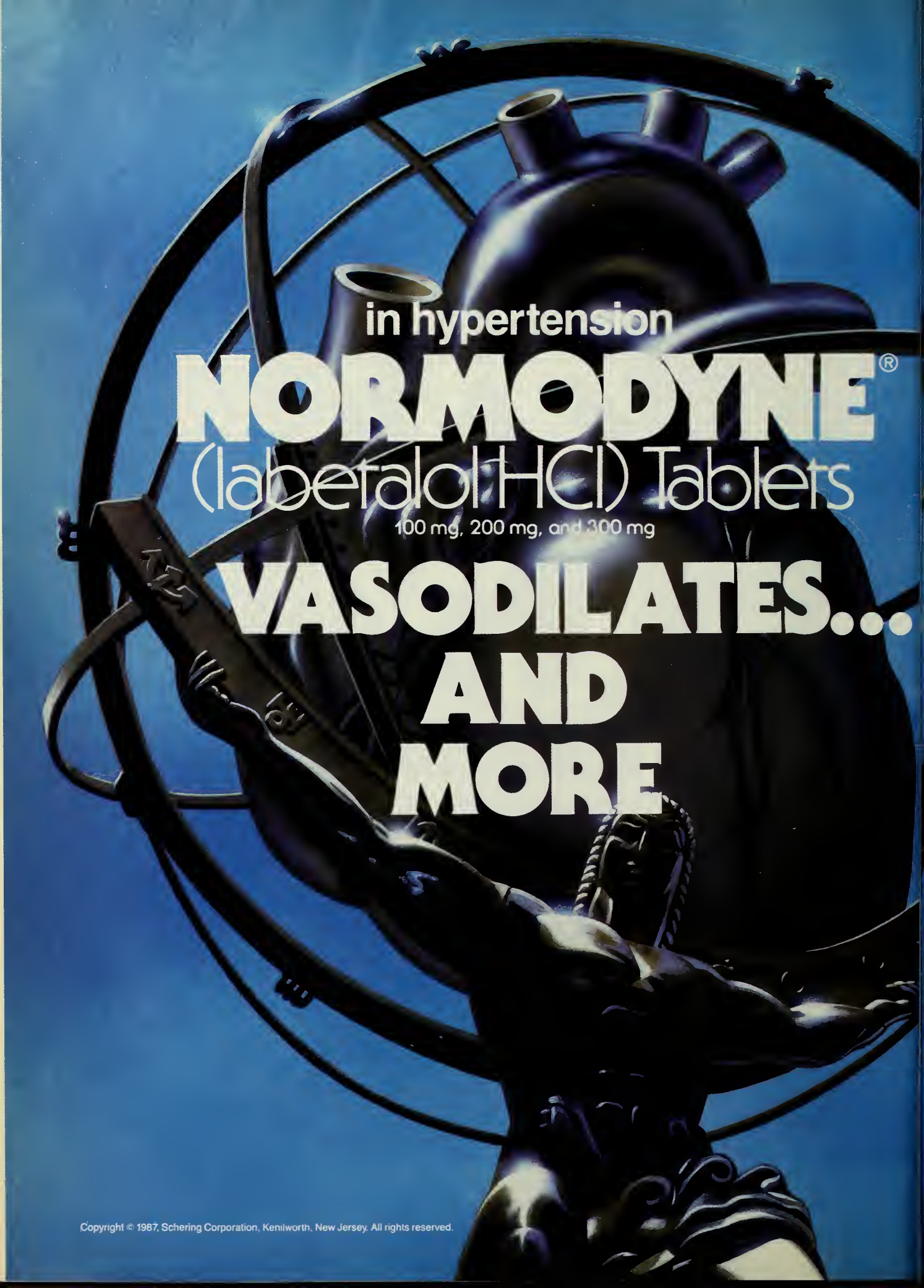
- *Patient Billing*
- *Accounts Receivable*
- *Practice Analysis*
- *Insurance Forms Formatter*
- *Appointment Scheduling*
- *Report Generator*
- *Electronic Forms Submission*
- *Word Processing*
- *General Ledger*
- *Accounts Payable*
- *Payroll*
- *Supply Inventory*
- *Telecommunications*

## Expandability

Expansion can take place at any time...the user may add terminals and printers, increase the storage capacity, and install additional software modules without modification of existing operational procedures. This Medical Practice Management System grows to match your needs.

**S Y Z Y G Y®**
Computer Systems, Inc.
446 Borrego Court, San Dimas, CA 91773

*FOR MORE INFORMATION PLEASE CALL*
(800) 824-0532
(818) 332-3320




Copyright © 1987, Schering Corporation, Kenilworth, New Jersey. All rights reserved.

Schering

# Supports your patients' vital organs

- lowers blood pressure by reducing total peripheral resistance
- does not adversely affect heart rate and maintains cardiac output
- beta blockade minimizes risk of reflex tachycardia
- produces no adverse effect on HDL, cholesterol, or triglycerides
- does not impair renal function

# ...and supports your patients' life-styles

- maintains exercise capacity yet blunts surges in heart rate
- demonstrates a low incidence of impotence, fatigue, and cold extremities*

*Most adverse effects are mild, transient, and occur early in the course of treatment. In controlled clinical trials of three to four months' duration, the most common side effects noted in treating mild to moderate hypertension with NORMODYNE (labetalol HCl) Tablets include dizziness (11%), nausea (6%), and fatigue (5%). Dyspepsia (3%), nasal stuffiness (3%), impotence (1%), and drowsiness (<1%) have occurred to a lesser degree. Overall, reports of symptomatic postural hypotension have been uncommon and have included rare instances of syncope. For complete side effects profile, see Prescribing Information.

# NORMODYNE®
## (labetalol HCl) Tablets

For Brief Summary, please see following page.

13071942-JBS

**PRODUCT INFORMATION**

# NORMODYNE®

**brand of labetalol hydrochloride**

## Tablets

BRIEF SUMMARY

### INDICATIONS AND USAGE

NORMODYNE (labetalol HCl) Tablets are indicated in the management of hypertension. NORMODYNE Tablets may be used alone or in combination with other antihypertensive agents, especially thiaride and loop diuretics.

### CONTRAINDICATIONS

NORMODYNE (labetalol HCl) Tablets are contraindicated in bronchial asthma, overt cardiac failure, greater than first degree heart block, cardiogenic shock, and severe bradycardia (see **WARNINGS**).

### WARNINGS

*Cardiac Failure* Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure. Beta blockade carries a potential hazard of further depressing myocardial contractility and precipitating more severe failure. Although beta-blockers should be avoided in overt congestive heart failure, if necessary, labetalol HCl can be used with caution in patients with a history of heart failure who are well-compensated. Congestive heart failure has been observed in patients receiving labetalol HCl. Labetalol HCl does not abolish the inotropic action of digitalis on heart muscle.

*In Patients Without a History of Cardiac Failure* In patients with latent cardiac insufficiency, continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or be given a diuretic, and the response observed closely. If cardiac failure continues, despite adequate digitalization and diuretic, NORMODYNE (labetalol HCl) therapy should be withdrawn (gradually if possible).

*Exacerbation of Ischemic Heart Disease Following Abrupt Withdrawal* Angina pectoris has not been reported upon labetalol HCl discontinuation. However, hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred after *abrupt* discontinuation of such therapy. When discontinuing chronically administered NORMODYNE (labetalol HCl), particularly in patients with ischemic heart disease, the dosage should be gradually reduced over a period of one to two weeks and the patient should be carefully monitored. If angina markedly worsens or acute coronary insufficiency develops, NORMODYNE (labetalol HCl) administration should be reinstituted promptly, at least temporarily, and other measures appropriate for the management of unstable angina should be taken. Patients should be warned against interruption or discontinuation of therapy without the physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue NORMODYNE (labetalol HCl) therapy abruptly even in patients treated only for hypertension.

**Nonallergic Bronchospasm (e.g., chronic bronchitis and emphysema) Patients with bronchospastic disease should, in general, not receive beta-blockers.** NORMODYNE may be used with caution, however, in patients who do not respond to, or cannot tolerate, other antihypertensive agents. It is prudent, if NORMODYNE is used, to use the smallest effective dose, so that inhibition of endogenous or exogenous beta-agonists is minimized.

*Pheochromocytoma* Labetalol HCl has been shown to be effective in lowering the blood pressure and relieving symptoms in patients with pheochromocytoma. However, paradoxical hypertensive responses have been reported in a few patients with this tumor; therefore, use caution when administering labetalol HCl to patients with pheochromocytoma.

*Diabetes Mellitus and Hypoglycemia* Beta-adrenergic blockade may prevent the appearance of premonitory signs and symptoms (e.g., tachycardia) of acute hypoglycemia. This is especially important with labile diabetics. Beta-blockade also reduces the release of insulin in response to hyperglycemia; it may therefore be necessary to adjust the dose of antidiabetic drugs.

*Major Surgery* The necessity or desirability of withdrawing beta-blocking therapy prior to major surgery is controversial. Protracted severe hypotension and difficulty in restarting or maintaining a heart beat have been reported with beta-blockers. The effect of labetalol HCl's alpha-adrenergic activity has not been evaluated in this setting.

A synergism between labetalol HCl and halothane anesthesia has been shown (see **Drug Interactions**).

### PRECAUTIONS

**General** *Impaired Hepatic Function* NORMODYNE (labetalol HCl) Tablets should be used with caution in patients with impaired hepatic function since metabolism of the drug may be diminished.

*Jaundice or Hepatic Dysfunction* On rare occasions, labetalol HCl has been associated with jaundice (both hepatic and cholestatic). It is therefore recommended that treatment with labetalol HCl be stopped immediately should a patient develop jaundice or laboratory evidence of liver injury. Both have been shown to be reversible on stopping therapy.

**Information for Patients**

As with all drugs with beta-blocking activity, certain advice to patients being treated with labetalol HCl is warranted. This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects. While no incident of the abrupt withdrawal phenomenon (exacerbation of angina pectoris) has been reported with labetalol HCl, dosing with NORMODYNE Tablets should not be interrupted or discontinued without a physician's advice. Patients being treated with NORMODYNE Tablets should consult a physician at any sign of impending cardiac failure. Also, transient scalp tingling may occur, usually when treatment with NORMODYNE Tablets is initiated (see **ADVERSE REACTIONS**).

**Laboratory Tests**

As with any new drug given over prolonged periods, laboratory parameters should be observed over regular intervals. In patients with concomitant illnesses, such as impaired renal function, appropriate tests should be done to monitor these conditions.

**Drug Interactions**

In one survey, 2.3% of patients taking labetalol HCl in combination with tricyclic antidepressants experienced tremor as compared to 0.7% reported to occur with labetalol HCl alone. The contribution of each of the treatments to this adverse reaction is unknown but the possibility of a drug interaction cannot be excluded.

Drugs possessing beta-blocking properties can blunt the bronchodilator effect of beta-receptor agonist drugs in patients with bronchospasm; therefore, doses greater than the normal anti-asthmatic dose of beta-agonist bronchodilator drugs may be required.

Cimetidine has been shown to increase the bioavailability of labetalol HCl. Since this could be explained either by enhanced absorption or by an alteration of hepatic metabolism of labetalol HCl, special care should be used in establishing the dose required for blood pressure control in such patients.

Synergism has been shown between halothane anesthesia and intravenously administered labetalol HCl. During controlled hypotensive anesthesia using labetalol HCl in association with halothane, high concentrations (3% or above) of halothane should not be used because the degree of hypotension will be increased and because of the possibility of a large reduction in cardiac output and an increase in central venous pressure. The anesthesiologist should be informed when a patient is receiving labetalol HCl.

Labetalol HCl blunts the reflex tachycardia produced by nitroglycerin without preventing its hypotensive effect. If labetalol HCl is used with nitroglycerin in patients with angina pectoris, additional antihypertensive effects may occur.

**Drug/Laboratory Test Interactions**

The presence of a metabolite of labetalol in the urine may result in falsely increased levels of urinary catecholamines when measured by a nonspecific trihydroxyindole (THI) reaction. In screening patients suspected of having a pheochromocytoma and being treated with labetalol HCl, specific radioenzymatic or high performance liquid chromatography assay techniques should be used to determine levels of catecholamines or their metabolites.

**Carcinogenesis, Mutagenesis, Impairment of Fertility**

Long-term oral dosing studies with labetalol HCl for 18 months in mice and for 2 years in rats showed no evidence of carcinogenesis. Studies with labetalol HCl, using dominant lethal assays in rats and mice, and exposing microorganisms according to modified Ames tests, showed no evidence of mutagenesis.

**Pregnancy Category C**

Teratogenic studies have been performed with labetalol in rats and rabbits at oral doses up to approximately 6 and 4 times the maximum recommended human dose (MRHD), respectively. No reproducible evidence of fetal malformations was observed. Increased fetal resorptions were seen in both species at doses approximating the MRHD. There are no adequate and well-controlled studies in pregnant women. Labetalol should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

**Nonteratogenic Effects**

Infants of mothers who were treated with labetalol HCl for hypertension during pregnancy did not appear to be adversely affected by the drug. Oral administration of labetalol to rats during late gestation through weaning at doses of 2 to 4 times the MRHD caused a decrease in neonatal survival.

**Labor and Delivery**

Labetalol HCl given to pregnant women with hypertension did not appear to affect the usual course of labor and delivery.

**Nursing Mothers**

Small amounts of labetalol (approximately 0.004% of the maternal dose) are excreted in human milk. Caution should be exercised when NORMODYNE Tablets are administered to a nursing woman.

**Pediatric Use**

Safety and effectiveness in children have not been established.

### ADVERSE REACTIONS

Most adverse effects are mild, transient and occur early in the course of treatment. In controlled clinical trials of 3 to 4 months duration, discontinuation of NORMODYNE (labetalol HCl) Tablets due to one or more adverse effects was required in 7% of all patients. In these same trials, beta-blocker control agents led to discontinuation in 8 to 10% of patients, and a centrally acting alpha-agonist in 30% of patients.

The incidence rates of adverse reactions listed in the following table were derived from multicenter controlled clinical trials, comparing labetalol HCl, placebo, metoprolol and propranolol, over treatment periods of 3 and 4 months. Where the frequency of adverse effects for labetalol HCl and placebo is similar, causal relationship is uncertain. The rates are based on adverse reactions considered probably drug-related by the investigator. If all reports are considered, the rates are somewhat higher (e.g., dizziness 20%, nausea 14%, fatigue 11%), but the overall conclusions are unchanged.

| | Labetalol HCl (N = 227) % | Placebo (N = 98) % | Propranolol (N = 84) % | Metoprolol (N = 49) % |
|---|---|---|---|---|
| Body as a whole | | | | |
| fatigue | 5 | 0 | 12 | 12 |
| asthenia | 1 | 1 | 1 | 0 |
| headache | 2 | 1 | 1 | 2 |
| Gastrointestinal | | | | |
| nausea | 6 | 1 | 1 | 2 |
| vomiting | <1 | 0 | 0 | 0 |
| dyspepsia | 3 | 1 | 1 | 0 |
| abdominal pain | 0 | 0 | 1 | 2 |
| diarrhea | <1 | 0 | 2 | 0 |
| taste distortion | 1 | 0 | 0 | 0 |
| Central and Peripheral Nervous Systems | | | | |
| dizziness | 11 | 3 | 4 | 4 |
| paresthesias | <1 | 0 | 0 | 0 |
| drowsiness | <1 | 2 | 2 | 2 |
| Autonomic Nervous System | | | | |
| nasal stuffiness | 3 | 0 | 0 | 0 |
| ejaculation failure | 2 | 0 | 0 | 0 |
| impotence | 1 | 0 | 1 | 3 |
| increased sweating | <1 | 0 | 0 | 0 |
| Cardiovascular | | | | |
| edema | 1 | 0 | 0 | 0 |
| postural hypotension | 1 | 0 | 0 | 0 |
| bradycardia | 0 | 0 | 5 | 12 |
| Respiratory | | | | |
| dyspnea | 2 | 0 | 1 | 2 |
| Skin | | | | |
| rash | 1 | 0 | 0 | 0 |
| Special Senses | | | | |
| vision abnormality | 1 | 0 | 0 | 0 |
| vertigo | 2 | 1 | 0 | 0 |

The adverse effects were reported spontaneously and are representative of the incidence of adverse effects that may be observed in a properly selected hypertensive patient population, i.e., a group excluding patients with bronchospastic disease, overt congestive heart failure, or other contraindications to beta-blocker therapy.

Clinical trials also included studies utilizing daily doses up to 2400 mg in more severely hypertensive patients. Certain of the side effects increased with increasing dose as shown in the table below which depicts the entire U.S. therapeutic trials data base for adverse reactions that are clearly or possibly dose related.

| Labetalol HCl Daily Dose (mg) | 200 | 300 | 400 | 600 |
|---|---|---|---|---|
| Number of Patients | 522 | 181 | 606 | 608 |
| Dizziness (%) | 2 | 3 | 3 | 3 |
| Fatigue | 2 | 1 | 4 | 4 |
| Nausea | <1 | 0 | 1 | 2 |
| Vomiting | 0 | 0 | <1 | <1 |
| Dyspepsia | 1 | 0 | 2 | 1 |
| Paresthesias | 2 | 0 | 2 | 2 |
| Nasal Stuffiness | 1 | 1 | 2 | 2 |
| Ejaculation Failure | 0 | 2 | 1 | 2 |
| Impotence | 1 | 1 | 1 | 1 |
| Edema | 1 | 0 | 1 | 1 |

| Labetalol HCl Daily Dose (mg) | 800 | 900 | 1200 | 1600 | 2400 |
|---|---|---|---|---|---|
| Number of Patients | 503 | 117 | 411 | 242 | 175 |
| Dizziness (%) | 5 | 1 | 9 | 13 | 16 |
| Fatigue | 5 | 3 | 7 | 6 | 10 |
| Nausea | 4 | 0 | 7 | 11 | 19 |
| Vomiting | <1 | 0 | 1 | 2 | 3 |
| Dyspepsia | 1 | 0 | 2 | 2 | 4 |
| Paresthesias | 1 | 1 | 2 | 5 | 5 |
| Nasal Stuffiness | 2 | 2 | 4 | 5 | 6 |
| Ejaculation Failure | 3 | 0 | 4 | 3 | 5 |
| Impotence | 2 | 4 | 3 | 4 | 3 |
| Edema | 1 | 0 | 1 | 2 | 2 |

In addition, a number of other less common adverse events have been reported in clinical trials or the literature:

*Cardiovascular* Postural hypotension, including rarely, syncope.

*Central and Peripheral Nervous Systems* Paresthesias, most frequently described as scalp tingling. In most cases, it was mild, transient and usually occurred at the beginning of treatment.

*Collagen Disorders* Systemic lupus erythematosus; positive antinuclear factor (ANF).

*Eyes* Dry eyes.

*Immunological System* Antimitochondrial antibodies.

*Liver and Biliary System* Cholestasis with or without jaundice.

*Musculo-Skeletal System* Muscle cramps; toxic myopathy.

*Respiratory System* Bronchospasm.

*Skin and Appendages* Rashes of various types, such as generalized maculo-papular; lichenoid; urticarial; bullous lichen planus; psoriaform; facial erythema; Peyronie's disease; reversible alopecia.

*Urinary System* Difficulty in micturition, including acute urinary bladder retention.

Following approval for marketing in the United Kingdom, a monitored release survey involving approximately 6,800 patients was conducted for further safety and efficacy evaluation of this product. Results of this survey indicate that the type, severity, and incidence of adverse effects were comparable to those cited above.

**Potential Adverse Effects**

In addition, other adverse effects not listed above have been reported with other beta-adrenergic blocking agents.

*Central Nervous System* Reversible mental depression progressing to catatonia; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

*Cardiovascular* Intensification of AV block. See **CONTRAINDICATIONS.**

*Allergic* Fever combined with aching and sore throat; laryngospasm; respiratory distress.

*Hematologic* Agranulocytosis; thrombocytopenic or nonthrombocytopenic purpura.

*Gastrointestinal* Mesenteric artery thrombosis; ischemic colitis.

The oculomucocutaneous syndrome associated with the beta-blocker practolol has not been reported with labetalol HCl.

**Clinical laboratory tests:** There have been reversible increases of serum transaminases in 4% of patients treated with labetalol HCl and tested, and more rarely, reversible increases in blood urea.

### OVERDOSAGE

Overdosage with NORMODYNE (labetalol HCl) Tablets causes excessive hypotension which is posture sensitive, and sometimes, excessive bradycardia. Patients should be laid supine and their legs raised if necessary to improve the blood supply to the brain. The following additional measures should be employed if necessary: *Excessive bradycardia* — administer atropine (3.0 mg). If there is no response to vagal blockade, administer isoproterenol cautiously. *Cardiac failure* — administer a digitalis glycoside and a diuretic. *Hypotension* — administer vasopressors, e.g., norepinephrine. There is pharmacological evidence that norepinephrine may be the drug of choice. *Bronchospasm* — administer a beta$_2$-stimulating agent and/or a theophylline preparation.

Gastric lavage or pharmacologically induced emesis (using syrup of ipecac) is useful for removal of the drug shortly after ingestion. Labetalol HCl can be removed from the general circulation by hemodialysis.

The oral $LD_{50}$ value of labetalol HCl in the mouse is approximately 600 mg/kg and in the rat is greater than 2 gm/kg. The intravenous $LD_{50}$ in these species is 50 to 60 mg/kg.

### DOSAGE AND ADMINISTRATION

DOSAGE MUST BE INDIVIDUALIZED. The recommended initial dose is 100 mg twice daily whether used alone or added to a diuretic regimen. After 2 or 3 days, using standing blood pressure as an indicator, dosage may be titrated in increments of 100 mg bid every 2 or 3 days. The usual maintenance dosage of labetalol HCl is between 200 and 400 mg twice daily.

Since the full antihypertensive effect of labetalol HCl is usually seen within the first one to three hours of the initial dose or dose increment, the assurance of a lack of an exaggerated hypotensive response can be clinically established in the office setting. The antihypertensive effects of continued dosing can be measured at subsequent visits, approximately 12 hours after a dose, to determine whether further titration is necessary.

Patients with severe hypertension may require from 1200 mg to 2400 mg per day, with or without thiaride diuretics. Should side effects (principally nausea or dizziness) occur with these doses administered bid, the same total daily dose administered three times daily may improve tolerability and facilitate further titration. Titration increments should not exceed 200 mg twice daily.

When a diuretic is added, an additive antihypertensive effect can be expected. In some cases this may necessitate a labetalol HCl dosage adjustment. As with most antihypertensive drugs, optimal dosages of NORMODYNE Tablets are usually lower in patients also receiving a diuretic.

When transferring patients from other antihypertensive drugs, NORMODYNE Tablets should be introduced as recommended and the dosage of the existing therapy progressively decreased.

### HOW SUPPLIED

NORMODYNE (labetalol HCl) Tablets, 100 mg, light-brown, round, scored, film-coated tablets engraved on one side with Schering and product identification numbers 244, and on the other side the number 100 for the strength and "NORMODYNE"; bottles of 100 (NDC-0085-0244-04), 500 (NDC-0085-0244-05), and box of 100 for unit-dose dispensing (NDC-0085-0244-08).

NORMODYNE (labetalol HCl) Tablets, 200 mg, white, round, scored, film-coated tablets engraved on one side with Schering and product identification numbers 752, and on the other side the number 200 for the strength and "NORMODYNE"; bottles of 100 (NDC-0085-0752-04), 500 (NDC-0085-0752-05), box of 100 for unit-dose dispensing (NDC-0085-0752-08), and Patient Calendar Package of 56 (4 bottles of 14 tablets) (NDC-0085-0752-03).

NORMODYNE (labetalol HCl) Tablets, 300 mg, blue, round, film-coated tablets engraved on one side with Schering and product identification numbers 438, and on the other side the number 300 for the strength and "NORMODYNE"; bottles of 100 (NDC-0085-0438-03), 500 (NDC-0085-0438-05), box of 100 for unit-dose dispensing (NDC-0085-0438-06), and Patient Calendar Package of 56 (4 bottles of 14 tablets) (NDC-0085-0438-02).

**NORMODYNE (labetalol HCl) Tablets should be stored between 2° and 30°C (36° and 86°F).**

**NORMODYNE (labetalol HCl) Tablets in the unit-dose boxes should be protected from excessive moisture.**

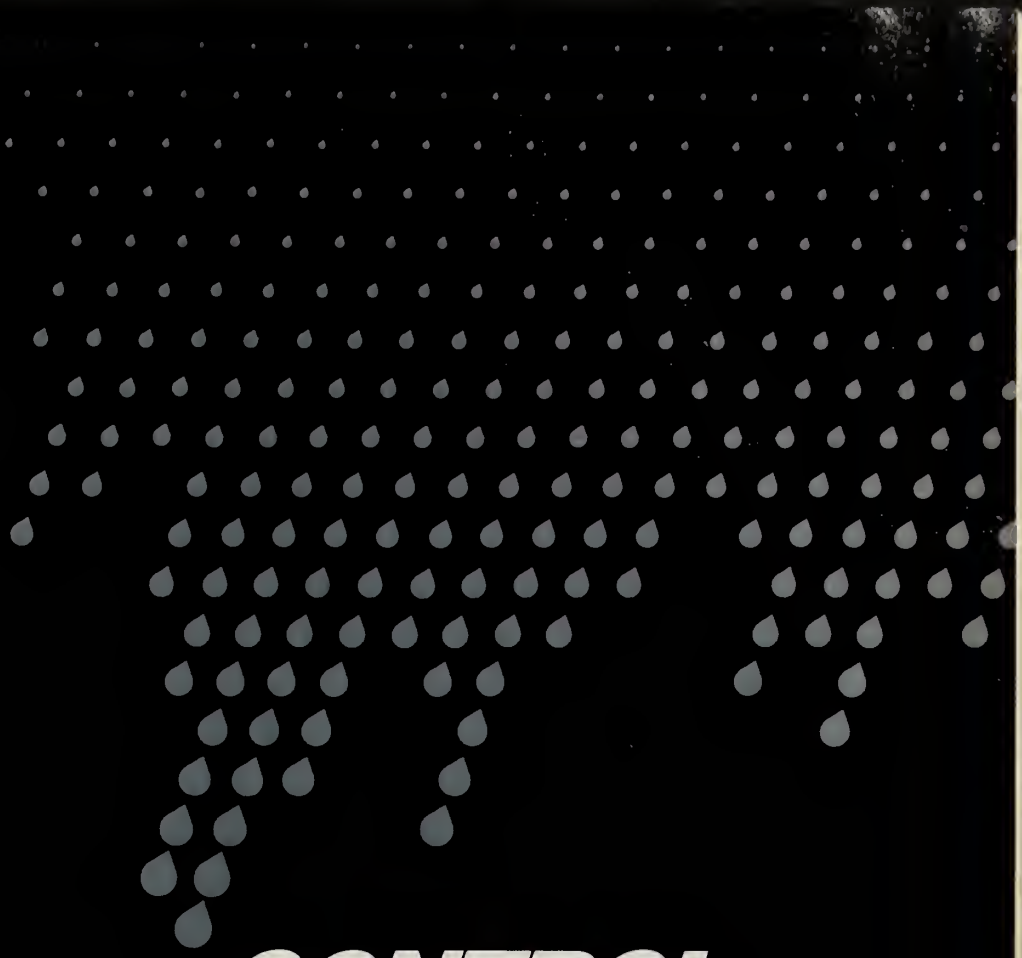
For complete prescribing information, please consult package insert.

Schering Corporation
Kenilworth, NJ 07033

Revised 3/85

Copyright © 1984, 1985, Schering Corporation. All rights reserved.

NR-542: 13963800



# CONTROL ACID RAIN

**with once-a-night h.s. therapy for active duodenal ulcers**

**Zantac 300**

ranitidine HCl/Glaxo 300 mg tablets

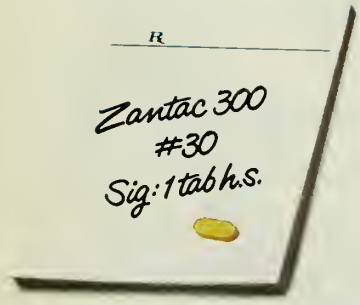
Glaxo ROCHE

See adjacent page for Brief Summary of Product Information

*In active duodenal ulcers*

# *Once-a-night h.s. therapy controls acid rain*

**Zantac 300**
ranitidine HCl/Glaxo 300 mg tablets




**ZANTAC® 150 Tablets**
**(ranitidine hydrochloride)**
**ZANTAC® 300 Tablets**
**(ranitidine hydrochloride)**

**BRIEF SUMMARY OF PRODUCT INFORMATION**

The following is a brief summary only. Before prescribing, see complete prescribing information in ZANTAC® product labeling.

**INDICATIONS AND USAGE:** ZANTAC® is indicated in:

1. Short-term treatment of **active duodenal ulcer**. Most patients heal within four weeks.
2. **Maintenance therapy** for duodenal ulcer patients at reduced dosage after healing of acute ulcers.
3. The treatment of **pathological hypersecretory conditions** (eg, Zollinger-Ellison syndrome and systemic mastocytosis).
4. Short-term treatment of **active, benign gastric ulcer**. Most patients heal within six weeks and the usefulness of further treatment has not been demonstrated.
5. Treatment of **gastroesophageal reflux disease (GERD)**. Symptomatic relief commonly occurs within one or two weeks after starting therapy and is maintained throughout a six-week course of therapy.

In active duodenal ulcer; active, benign gastric ulcer; hypersecretory states; and GERD, concomitant antacids should be given as needed for relief of pain.

**CONTRAINDICATIONS:** ZANTAC® is contraindicated for patients known to have hypersensitivity to the drug.

**PRECAUTIONS:** Symptomatic response to ZANTAC® therapy does not preclude the presence of gastric malignancy.

Since ZANTAC is excreted primarily by the kidney, dosage should be adjusted in patients with impaired renal function (see **DOSAGE AND ADMINISTRATION**). Caution should be observed in patients with hepatic dysfunction since ZANTAC is metabolized in the liver.

False-positive tests for urine protein with Multistix® may occur during ZANTAC therapy, and therefore testing with sulfosalicylic acid is recommended.

Although recommended doses of ZANTAC do not inhibit the action of cytochrome P-450 enzymes in the liver, there have been isolated reports of drug interactions which suggest that ZANTAC may affect the bioavailability of certain drugs by some mechanism as yet unidentified (eg, a pH-dependent effect on absorption or a change in volume of distribution).

Lack of experience to date precludes recommending ZANTAC for use in children or pregnant patients. Since ZANTAC is secreted in human milk, caution should be exercised when administered to a nursing mother.

**ADVERSE REACTIONS:** Headache, sometimes severe, seems to be related to ZANTAC® administration. Constipation, diarrhea, nausea/vomiting, and abdominal discomfort/pain have been reported. There have been rare reports of malaise, dizziness, somnolence, insomnia, vertigo, tachycardia, bradycardia, premature ventricular beats, and arthralgias. Rare cases of reversible mental confusion, agitation, depression, and hallucinations have been reported, predominantly in severely ill elderly patients.

In normal volunteers, SGPT values were increased to at least twice the pretreatment levels in 6 of 12 subjects receiving 100 mg qid IV for seven days, and in 4 of 24 subjects receiving 50 mg qid for five days. With oral administration there have been occasional reports of reversible hepatitis, hepatocellular or hepatocanalicular or mixed, with or without jaundice.

There have been rare reports of reversible leukopenia, granulocytopenia, thrombocytopenia, and pancytopenia.

Although controlled studies have shown no antiandrogenic activity, occasional cases of gynecomastia, impotence, and loss of libido have been reported in male patients receiving ZANTAC, but the incidence did not differ from that in the general population.

Incidents of rash, including rare cases suggestive of mild erythema multiforme, and, rarely, alopecia, have been reported, as well as rare cases of hypersensitivity reactions (eg, bronchospasm, fever, rash, eosinophilia) and small increases in serum creatinine.

**OVERDOSAGE:** Information concerning possible overdosage and its treatment appears in the full prescribing information.

**DOSAGE AND ADMINISTRATION: Active Duodenal Ulcer:** The current recommended adult oral dosage is 150 mg twice daily. An alternate dosage of 300 mg once daily at bedtime can be used for patients in whom dosing convenience is important. The advantages of one treatment regimen compared to the other in a particular patient population have yet to be demonstrated.

**Maintenance Therapy:** The current recommended adult oral dosage is 150 mg at bedtime.

**Pathological Hypersecretory Conditions (such as Zollinger-Ellison Syndrome):** The current recommended adult oral dosage is 150 mg twice a day. In some patients it may be necessary to administer ZANTAC 150-mg doses more frequently. Doses should be adjusted to individual patient needs, and should continue as long as clinically indicated. Doses up to 6 g/day have been employed in patients with severe disease.

**Benign Gastric Ulcer:** The current recommended adult oral dosage is 150 mg twice a day.

**GERD:** The current recommended adult oral dosage is 150 mg twice a day.

**Dosage Adjustment for Patients with Impaired Renal Function:** On the basis of experience with a group of subjects with severely impaired renal function treated with ZANTAC, the recommended dosage in patients with a creatinine clearance less than 50 ml/min is 150 mg every 24 hours. Should the patient's condition require, the frequency of dosing may be increased to every 12 hours or even further with caution. Hemodialysis reduces the level of circulating ranitidine. Ideally, the dosage schedule should be adjusted so that the timing of a scheduled dose coincides with the end of hemodialysis.

**HOW SUPPLIED:** ZANTAC® 300 Tablets (ranitidine hydrochloride equivalent to 300 mg of ranitidine) are yellow, capsule-shaped tablets embossed with "ZANTAC 300" on one side and "Glaxo" on the other. They are available in bottles of 30 (NDC 0173-0393-40) and unit dose packs of 100 tablets (NDC 0173-0393-47).

ZANTAC® 150 Tablets (ranitidine hydrochloride equivalent to 150 mg of ranitidine) are white tablets embossed with "ZANTAC 150" on one side and "Glaxo" on the other. They are available in bottles of 60 tablets (NDC 0173-0344-42) and unit dose packs of 100 tablets (NDC 0173-0344-47).

**Store between 15° and 30°C (59° and 86°F) in a dry place. Protect from light. Replace cap securely after each opening.**

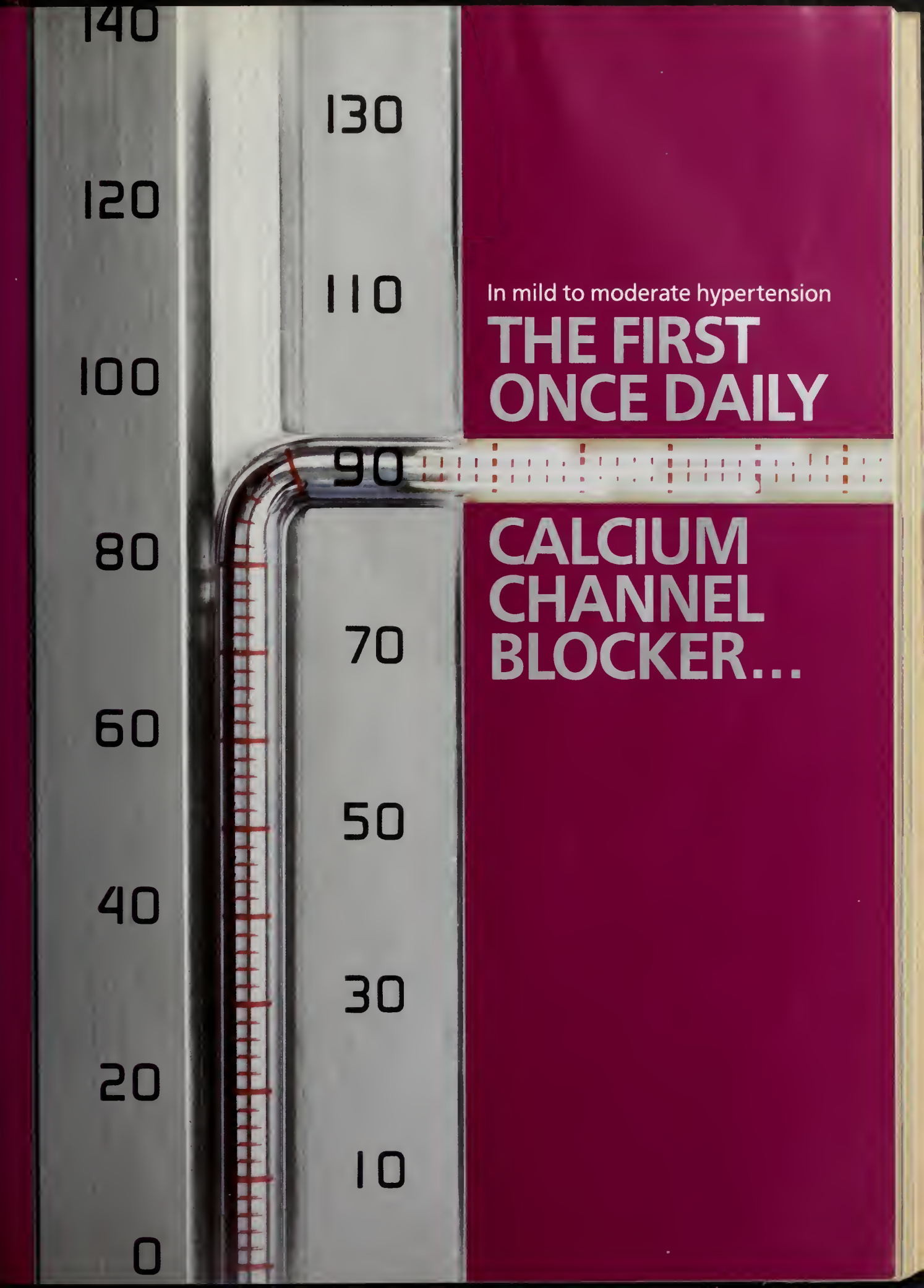
© Copyright 1983, Glaxo Inc. All rights reserved. October 1986

**Glaxo**
Glaxo Inc.
Research Triangle Park, NC 27709

© 1987, Glaxo Inc.

ZAN325R

January 1987


140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
In mild to moderate hypertension
THE FIRST ONCE DAILY
CALCIUM CHANNEL BLOCKER...

**NEW**
ONCE DAILY

# ISOPTIN SR*

## (verapamil HCl/Knoll)

***240 mg scored, sustained-release tablets***

**JAMES B.**
38, black male, heavy smoker. Prescribed a diuretic by another physician last year for hypertension.

**YOUR CONCERNS**
Presents with "smoker's cough." Workup reveals a BP of 150/107.

**A LOGICAL CHOICE FOR CONTROL OF HIS BP**
ISOPTIN* (verapamil HCl/Knoll) because...
— Black hypertensives often have low plasma renin activity and generally do not respond favorably to beta blockers.
— Beta blockers may increase the likelihood of bronchospasm.

**ALICE W.**
65, diabetic, overweight. Her BP has elevated to 190/98.

**YOUR CONCERNS**
She's on daily insulin.

**A LOGICAL CHOICE FOR CONTROL OF HER BP**
ISOPTIN* (verapamil HCl/Knoll) because...
— Unlike most beta blockers and diuretics, ISOPTIN has no adverse effects on serum glucose levels.
— Unlike most beta blockers, ISOPTIN does not mask the symptoms of hypoglycemia.

**THOMAS G.**
70, asthmatic. In the past, BP adequately controlled with 25 mg hydrochlorothiazide daily.

**YOUR CONCERNS**
Today patient presents with symptoms of gout. Workup reveals high uric acid level, low serum potassium, and BP elevated to 180/98.

**A LOGICAL CHOICE FOR CONTROL OF HIS BP**
ISOPTIN* (verapamil HCl/Knoll) because...
— Unlike diuretics, ISOPTIN will not decrease serum potassium levels or elevate uric acid levels.
— Unlike beta blockers, ISOPTIN can be used safely in asthma and COPD patients.

**JOHN K.**
42, Annual physical uncovered diastolic BP of 102... confirmed on three successive office visits. Unresponsive to nonpharmacologic intervention.

**YOUR CONCERNS**
Salesman, spends many hours of his working day in car... total cholesterol level 300, HDL 35.

**A LOGICAL CHOICE FOR CONTROL OF HIS BP**
ISOPTIN* (verapamil HCl/Knoll) because...
— Unlike diuretics, ISOPTIN does not cause urinary urgency.
— Unlike either beta blockers or diuretics, ISOPTIN will not adversely affect his already seriously compromised lipid profile.
— Unlike with propranolol, fatigue and impotence are rarely reported.

## *Antihypertensive therapy you and your patients can live with*

*A product of Knoll research.

© 1986, BASF K & F Corporation

2538/2-87

Knoll Pharmaceuticals
A Unit of BASF K&F Corporation
Whippany, New Jersey 07981

BASF Group

knoll®

Printed in U.S.A.

Please see adjacent page for brief summary.

*In mild to moderate hypertension* Brief Summary

***THE FIRST ONCE DAILY CALCIUM CHANNEL BLOCKER***

**ISOPTIN® SR (verapamil HCl/Knoll) 240 mg scored, sustained-release tablets**

**CONTRAINDICATIONS:** 1) Severe left ventricular dysfunction (see WARNINGS), 2) Hypotension (less than 90 mmHg systolic pressure) or cardiogenic shock, 3) Sick sinus syndrome or 2nd or 3rd degree AV block (except in patients with a functioning artificial ventricular pacemaker).

**WARNINGS: Heart Failure:** ISOPTIN should be avoided in patients with severe left ventricular dysfunction (see DRUG INTERACTIONS). Patients with milder ventricular dysfunction should, if possible, be controlled before verapamil treatment. Hypotension: ISOPTIN (verapamil HCl) may produce occasional symptomatic hypotension. Elevated Liver Enzymes: Elevations of transaminases with and without concomitant elevations in alkaline phosphatase and bilirubin have been reported. Periodic monitoring of liver function in patients receiving verapamil is therefore prudent. Accessory Bypass Tract (Wolff-Parkinson-White): Patients with paroxysmal and/or chronic atrial flutter or atrial fibrillation and a coexisting accessory AV pathway have developed increased antegrade conduction across the accessory pathway producing a very rapid ventricular response or ventricular fibrillation after receiving intravenous verapamil. While this has not been reported with oral verapamil, it should be considered a potential risk. Treatment is usually D.C.-cardioversion. Atrioventricular Block: The effect of verapamil on AV conduction and the SA node may cause asymptomatic 1st degree AV block and transient bradycardia. Higher degrees of AV block, while infrequent (0.8%), may require a reduction in dosage or, in rare instances, discontinuation of verapamil HCl. Patients with Hypertrophic Cardiomyopathy (IHSS): Although verapamil has been used in the therapy of patients with IHSS, severe cardiovascular decompensation and death have been noted in this patient population.

**PRECAUTIONS: Impaired Hepatic or Renal Function:** Verapamil is highly metabolized by the liver with about 70% of an administered dose excreted in the urine. In patients with impaired hepatic or renal function verapamil should be administered cautiously and the patients monitored for abnormal prolongation of the PR interval or other signs of excessive pharmacological effects (see OVERDOSAGE).

**Drug Interactions:** Beta Blockers: Concomitant use of ISOPTIN and oral beta-adrenergic blocking agents may be beneficial in certain patients with chronic stable angina or hypertension, but available information is not sufficient to predict with confidence the effects of concurrent treatment in patients with left ventricular dysfunction or cardiac conduction abnormalities. Digitalis: Clinical use of verapamil in digitalized patients has shown the combination to be well tolerated if digoxin doses are properly adjusted. However, chronic verapamil treatment increases serum digoxin levels by 50 to 75% during the first week of therapy and this can result in digitalis toxicity. Upon discontinuation of ISOPTIN (verapamil HCl), the patient should be reassessed to avoid underdigitalization. Antihypertensive Agents: Verapamil administered concomitantly with oral antihypertensive agents (e.g., vasodilators, angiotensin-converting enzyme inhibitors, diuretics, beta blockers, prazosin) will usually have an additive effect on lowering blood pressure. Patients receiving these combinations should be appropriately monitored. Disopyramide: Disopyramide should not be administered within 48 hours before or 24 hours after verapamil administration. Quinidine: In patients with hypertrophic cardiomyopathy (IHSS), concomitant use of verapamil and quinidine resulted in significant hypotension. There has been a report of increased quinidine levels during verapamil therapy. Nitrates: The pharmacologic profile of verapamil and nitrates as well as clinical experience suggest beneficial interactions. Cimetidine: Two clinical trials have shown a lack of significant verapamil interaction with cimetidine. A third study showed cimetidine reduced verapamil clearance and increased elimination to 1/2. Anesthetic Agents: Verapamil may potentiate the activity of neuromuscular blocking agents and inhalation anesthetics. Carbamazepine: Verapamil may increase carbamazepine concentrations during combined therapy. Rifampin: Therapy with rifampin may markedly reduce oral verapamil bioavailability. Lithium: Verapamil may lower lithium levels in patient on chronic oral lithium therapy. Carcinogenesis, Mutagenesis, Impairment of Fertility: There was no evidence of a carcinogenic potential of verapamil administered to rats for two years. Verapamil was not mutagenic in the Ames test. Studies in female rats did not show impaired fertility. Effects on male fertility have not been determined. Pregnancy (Category C): There are no adequate and well-controlled studies in pregnant women. ISOPTIN crosses the placental barrier and can be detected in umbilical vein blood at delivery. This drug should be used during pregnancy, labor, and delivery, only if clearly needed. Nursing Mothers: ISOPTIN is excreted in human milk, therefore, nursing should be discontinued while verapamil is administered. Pediatric Use: Safety and efficacy of ISOPTIN in children below the age of 18 years have not been established.

**ADVERSE REACTIONS:** Constipation 8.4%, dizziness 3.5%, nausea 2.7%, hypotension 2.5%, edema 2.1%, headache 1.9%, CHF/pulmonary edema 1.8%, fatigue 1.7%, bradycardia 1.4%, 3° AV block 0.8%, flushing 0.1%, elevated liver enzymes (see WARNINGS). The following reactions, reported in less than 1.0% of patients, occurred under conditions (open trials, marketing experience) where a causal relationship is uncertain; they are mentioned to alert the physician to a possible relationship: angina pectoris, arthralgia and rash, AV block, blurred vision, cerebrovascular accident, chest pain, claudication, confusion, diarrhea, dry mouth, dyspnea, ecchymosis or bruising, equilibrium disorders, exanthema, gastrointestinal distress, gingival hyperplasia, gynecomastia, hair loss, hyperkeratosis, impotence, increased urination, insomnia, macules, muscle cramps, myocardial infarction, palpitations, paresthesia, psychotic symptoms, purpura (vasculitis), shakiness, somnolence, spotty menstruation, sweating, syncope, urticaria. Treatment of Acute Cardiovascular Adverse Reactions: Whenever severe hypotension or complete AV block occur following oral administration of verapamil, the appropriate emergency measures should be applied immediately, e.g., intravenously administered isoproterenol HCl, levarterenol bitartrate, atropine (all in the usual doses), or calcium gluconate (10% solution). If further support is necessary, inotropic agents (dopamine or dobutamine) may be administered. Actual treatment and dosage should depend on the severity and the clinical situation and the judgment and experience of the treating physician.

**OVERDOSAGE:** Treatment of overdosage should be supportive. Beta-adrenergic stimulation or parenteral administration of calcium solutions may increase calcium ion flux across the slow channel, and have been used effectively in treatment of deliberate overdosage with verapamil. Clinically significant hypotensive reactions or fixed high degree AV block should be treated with vasopressor agents or cardiac pacing, respectively. Asystole should be handled by the usual measures including cardiopulmonary resuscitation.

**Knoll Pharmaceuticals**
A Unit of BASF K&F Corporation
Whippany, New Jersey 07981

knoll®

**BASF** Group

©1986, BASF K&F Corporation 2474/11/86 Printed in U.S.A.



# Books Received

*Books received by* THE WESTERN JOURNAL OF MEDICINE *are acknowledged in this column. Selections will be made for more extensive review in the interest of readers as space permits.*

**THE ANESTHESIA MACHINE**—Clayton Petty, MD, Professor of Anesthesiology, University of Utah School of Medicine, Salt Lake City. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1986. 225 pages, $29.50.

**ATLAS OF HEAD AND NECK SURGERY**—Carl E. Silver, MD, Professor, Department of Surgery, Albert Einstein College of Medicine, and Chief, Head and Neck Service, Montefiore Medical Center and Albert Einstein College of Medicine, Bronx, New York. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1986. 317 pages, $98.

**BIOSTATISTICS IN CLINICAL MEDICINE**—Joseph A. Ingelfinger, MD, Assistant Professor of Medicine, Boston University School of Medicine, and Associate Director, Section of General Internal Medicine, Boston City Hospital; Frederick Mosteller, PhD, Roger I. Lee Professor of Mathematical Statistics and Chairman, Department of Health Policy and Management, School of Public Health, Harvard University, Boston; Lawrence A. Thibodeau, PhD, Senior Manager, Price Waterhouse, New York, and James H. Ware, PhD, Professor of Biostatistics, School of Public Health, Harvard University, Boston. MacMillan Publishing Co, 1987. 330 pages, price not given (paperback).

**CARDIOVASCULAR EMERGENCIES—Volume 9 in Clinics in Emergency Medicine—**Edited by Joseph P. Ornato, MD, Associate Professor of Internal Medicine (Cardiology) and Chief, Section of Emergency Medicine of the Department of Internal Medicine, Medical College of Virginia, Virginia Commonwealth University, Richmond. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1986. 252 pages, $29.

**CARDIOVASCULAR PROBLEMS IN PEDIATRIC CRITICAL CARE—in Clinics in Critical Care Medicine series**—Edited by David B. Swedlow, MD, Assistant Professor of Anesthesia and Pediatrics, University of Pennsylvania School of Medicine, and Senior Anesthesiologist, Department of Anesthesia and Critical Care, Children's Hospital of Philadelphia, and Russell C. Raphaely, MD, Associate Professor of Anesthesia and Pediatrics, University of Pennsylvania School of Medicine, and Senior Anesthesiologist and Director, Pediatric Intensive Care Complex, Department of Anesthesia and Critical Care, Children's Hospital of Philadelphia. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1986. 302 pages, $42.

**CLINICAL GENETICS HANDBOOK**—National Genetics Foundation Inc; Ruth Y. Berini, Executive Editor, Eva Kahn, Editor. Medical Economics Books, Oradell, NJ 07649, 1987. 354 pages, price not given (paperback).

**COMMON SPORTS INJURIES IN YOUNGSTERS**—Richard B. Birrer, MD, MPH, Associate Professor of Family Practice, State University of New York Health Sciences Center at Brooklyn, and David B. Brecher, MD, Attending Physician, Department of Family Medicine, Mease Clinic Countryside, Safety Harbor, Florida. Medical Economics Books, Oradell, NY 07649, 1987. 139 pages, price not given (paperback).

**COMPUTED TOMOGRAPHY OF THE SPINE—DIAGNOSTIC EXERCISES**—Robert Kricun, MD, Department of Radiology, Lehigh Valley Hospital Center, Allentown, Pennsylvania, and Clinical Assistant Professor, Department of Radiology, Hospital University of Pennsylvania, Philadelphia, and Morrie E. Kricun, MD, Associate Professor, Department of Radiology, Orthopedic Radiology Section, Hospital University of Pennsylvania, Philadelphia. Aspen Publishers, Inc, 1600 Research Blvd, Rockville, MD 20850, 1987. 286 pages, $56.

**CONTINUING MEDICAL EDUCATION—A PRIMER**—Edited by Adrienne B. Rosof, Coordinator for Continuing Medical Education, Suffolk County Academy of Medicine, Happauge, NY, and William C. Felch, MD, Executive Vice President, Alliance for Continuing Medical Education (ACME). Praeger Publishers, 521 Fifth Ave, New York, NY 10175, 1986. 206 pages, price not given.

**CONTROVERSIES IN ULTRASOUND—Volume 20 in Clinics in Diagnostic Ultrasound—**Edited by John P. McGahan, MD, Associate Professor of Radiology and Chief, Section of Ultrasound, University of California, Davis, School of Medicine. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1986. 360 pages, $45.

**ELECTRODIAGNOSIS IN CLINICAL NEUROLOGY—Second Edition—**Edited by Michael J. Aminoff, MD, Professor of Neurology, University of California, San Francisco, School of Medicine; Director, Clinical Neurophysiology Laboratories, and Attending Physician, University of California Medical Center, San Francisco. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1986. 736 pages, $79.

**EMERGENCIES IN OTOLARYNGOLOGY—**Edited by James Y. Suen, MD, Professor and Chairman, Department of Otolaryngology and Maxillofacial Surgery, University of Arkansas College of Medicine, and Stephen J. Wetmore, MD, Associate Professor and Vice Chairman, Department of Otolaryngology and Maxillofacial Surgery, University of Arkansas College of Medicine, and Chief of Otolaryngology, John L. McClellan Memorial Veterans Administration Medical Center, Little Rock. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1986. 250 pages, $30 (paperback).

**THE HUMAN PLACENTA—CLINICAL PERSPECTIVES—**Edited by J. Patrick Lavery, MD, Associate Professor, Department of Obstetrics and Gynecology, and Director, Division of Maternal-Fetal Medicine, University of Louisville School of Medicine, Louisville, Kentucky. Aspen Publishers, Inc, 1600 Research Blvd, Rockville, MD 20850, 1987. 279 pages, $59.

**HYPERCHOLESTEROLEMIA AND ATHEROSCLEROSIS—PATHOGENESIS AND PREVENTION—Volume 3 in Contemporary Issues in Endocrinology and Metabolism—**Edited by Daniel Steinberg, MD, PhD, Professor of Medicine, Department of Medicine, and Director, Specialized Center of Research on Arteriosclerosis, and Jerrold M. Olefsky, MD, Professor of Medicine, Department of Medicine, and Head, Division of Endocrinology and Metabolism, University of California, San Diego, School of Medicine, La Jolla. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1986. 256 pages, $36.

*(Continued on Page 516)*

# Continuing Medical Education

ARIZONA • CALIFORNIA, HAWAII, NEVADA • IDAHO • MONTANA • NEW MEXICO • UTAH • WASHINGTON • WYOMING

## ARIZONA

The following list of continuing medical education programs in Arizona is compiled by the Arizona Medical Association. All courses listed have been certified as meeting the criteria for Category I of the ArMA CME Certificate and the AMA Physicians Recognition Award. To list Category I continuing medical education programs, please send information to Arizona Medical Association, 810 West Bethany Home Road, Phoenix, AZ 85013; or phone (602) 246-8901.

Brochures and registration forms are available from the contact person or organization sponsoring the program.

April 22—**Current Perspectives: Wellness.** Arizona Medical Association, Phoenix. Wed. Contact: ArMA.

April 23—**Current Perspectives: Wellness.** VA Medical Center, Prescott. Thurs. Contact: ArMA.

April 24—**Clinical Aspect of Aging.** Fri. Contact: Dr Stonefeld, (602) 230-3479.

May 9-10—**Pathology of AIDS.** Loews Ventana Canyon Resort, Tucson. Sat-Sun. Contact: Beverly Richter for Arizona Society of Pathologists, (602) 246-8901.

June 4—**Arizona Medical Association Annual Scientific Session.** The Pointe at South Mountain, Phoenix. Thurs. Contact: ArMA.

June 12-14—**Pediatrics in the Red Rocks—10th Annual Summer Pediatrics Conference.** Poco Diablo Resort, Sedona. Fri-Sun. Contact: U of A.

### CONTACT INFORMATION

ArMA—Contact: Arizona Medical Association, 810 W Bethany Home Rd, Phoenix, AZ 85013. (602) 246-8901.

U of A—Contact: University of Arizona College of Medicine, Arizona Health Sciences Center, Tucson, AZ 85724. (602) 626-6707.

## CALIFORNIA, HAWAII AND NEVADA

This listing of continuing education programs in California, Hawaii and Nevada is supplied by the Committee on Continuing Medical Education of the California Medical Association. All courses and meetings listed have been approved for Category I credit toward the CMA Certificate in Continuing Medical Education. To have accredited courses listed here, please send information at least two months in advance to Department of Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690; or phone (415) 863-5522. For a list of organizations approved for Category I credit toward the CMA Certificate in Continuing Medical Education or for more information on accreditation or certification, please write to the above address.

### ANESTHESIOLOGY

April 26-May 1—**California Society of Anesthesiologists Hawaiian Seminar.** Sheraton Kauai Hotel, Poipu Beach, Hawaii. Sun-Fri. 21 hrs. $375. Contact: Linda P. Londerville, CSA, 100 S Ellsworth Ave, Ste 806, San Mateo 94401. (415) 348-1407.

May 1-3—**Clinical Neuromuscular Pharmacology—1987.** Anesthesiology Educational Foundation and UCLA at Palm Springs. Fri-Sun. 15 hrs. Contact: Anesthesiology Educational Foundation, PO Box 24230, Federal Bldg, Los Angeles 90024. (213) 825-0736.

June 25-28—**California Society of Anesthesiologists Annual Meeting.** Hotel Inter-Continental, San Diego. Thurs-Sun. 16 hrs. $225. Contact: Linda P. Londerville, 100 S Ellsworth Ave, Ste 806, San Mateo 94401. (415) 348-1407.

August 23-28—**California Society of Anesthesiologists Hawaiian Seminar.** Sheraton Royal Waikoloa Hotel, The Big Island, Hawaii. Sun-Fri. 20 hrs. $375. Contact: Linda P. Londerville, 100 S Ellsworth Ave, Ste 806, San Mateo 94401. (415) 348-1407.

September 12-13—**Case Conference on Clinical Anesthesiology.** California Society of Anesthesiologists at High Sierra Hotel, Lake Tahoe, Nevada. Sat-Sun. 9 hrs. $160. Contact: California Society of Anesthesiologists, 100 S Ellsworth Ave, Ste 806, San Mateo 94401. (415) 348-1407.

### CANCER

May 1—**1 Day Colon Cancer Screening and Flexible Sigmoidoscopy Workshop.** Continuing Medical Education Associates at Vacation Village Resort, San Diego. Fri. $175. Contact: J. Shiller, CMEA, PO Box 84296, San Diego 92138. (619) 223-2997.

May 3—**1 Day Colon Cancer Screening and Flexible Sigmoidoscopy Workshop.** Continuing Medical Education Associates at Holiday Inn Union Square, San Francisco. Sun. $175. Contact: J. Shiller, CMEA, PO Box 84296, San Diego 92138. (619) 223-2997.

### KEY TO ABBREVIATIONS

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690. (415) 863-5522.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Herbert M. Thomas, MD, MPH, Director of CME, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th Street, Los Angeles 90059. (213) 603-3183.

LLU: Loma Linda University
Contact: Varner J. Johns, Jr, MD, Associate Dean for Continuing Medical Education, Loma Linda University School of Medicine, Loma Linda 92354. (714) 796-7311, ext 2400.

PMC: Pacific Medical Center
Contact: Continuing Education, Pacific Medical Center, PO Box 7999, San Francisco 94120. (415) 563-4321, ext 2761.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Medical School Office Building, Suite X-365, Stanford 94305-6114. (415) 723-5594.

UCD: University of California, Davis
Contact: Ruth Feryok, Director, Office of Continuing Medical Education, University of California, Davis, School of Medicine, 2701 Stockton Boulevard, Sacramento 95817. (916) 453-5390.

UCI: University of California, Irvine
Contact: Melvin I. Marks, MD, Assistant Dean, University of California, Irvine, California College of Medicine, c/o UCI/CME Program, Memorial Medical Center, 2801 Atlantic Avenue, Long Beach 90801-1428. (213) 595-3811, or (714) 856-5414, UCI Extension.

UCLA: University of California, Los Angeles
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, PO Box 24902, UCLA, Los Angeles 90024. (213) 825-7241.

UCSD: University of California, San Diego
Contact: Office of Continuing Medical Education, University of California, San Diego, School of Medicine (M-017), La Jolla 92093. (619) 534-3713.

UCSF: University of California, San Francisco
Contact: Robert Maggio, Administrative Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 476-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 1975 Zonal Ave, KAM314, Los Angeles 90033. (213) 224-7051.

(Continued on Page 428)

# Paperless. Painless.

**Physicians Practice Management**
1810 S. Lynhurst, Suite Q
Indianapolis, Indiana 46241

© Copyright Physicians Practice Management, Inc., 1986

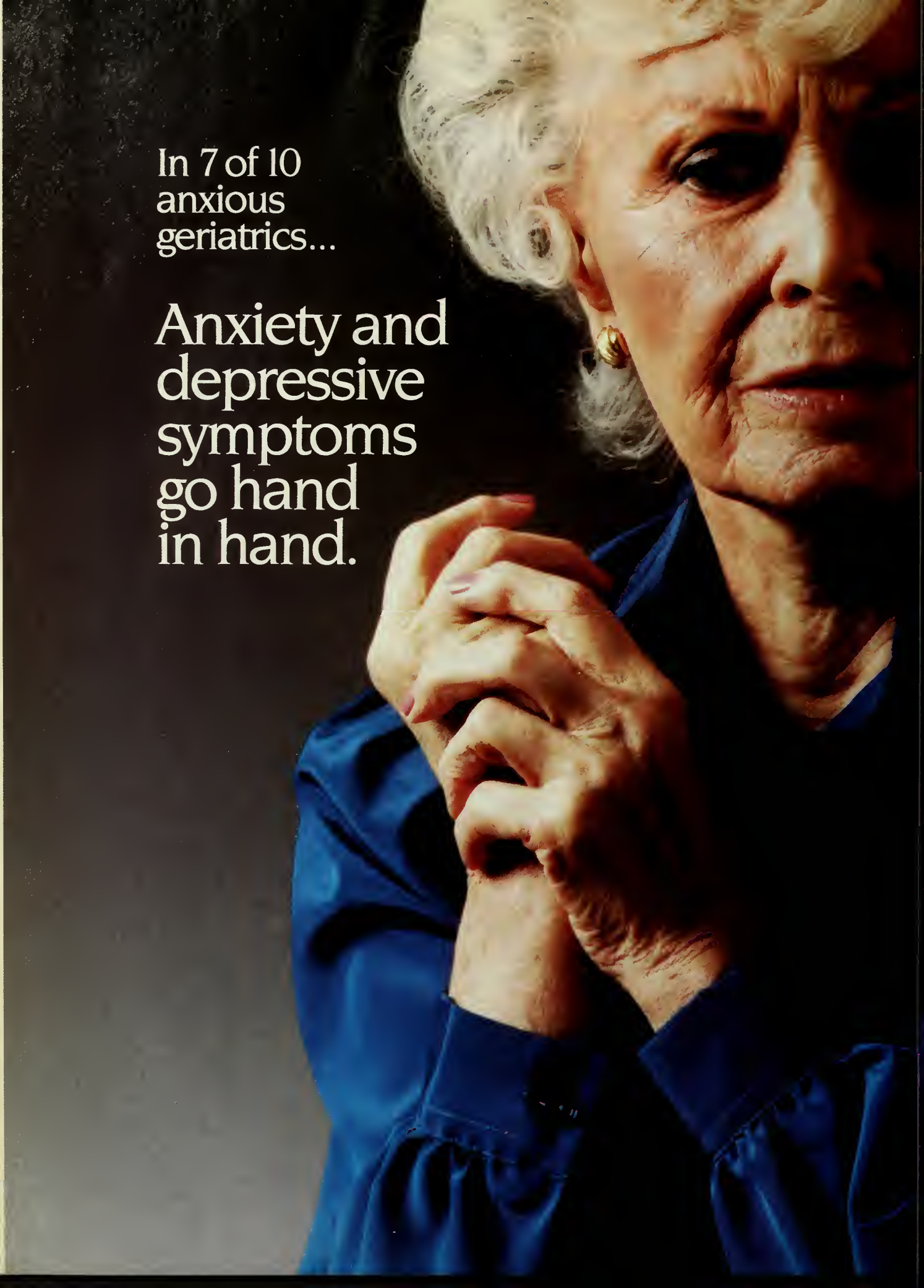
# Paid.

Processing stacks of insurance claims is time-consuming, tedious and costly. Errors can cause claim rejections, handling delays and slow reimbursement. ☐ Now, there's an easy, inexpensive way to control your processing paperwork. With PC*CLAIM™, the paperless program that electronically sends your claims to Medicare and other participating insurance companies. For only $89.95, you get the PC*CLAIM program, toll-free start-up support, and an unconditional, 30-day money-back guarantee. ☐ PPM offers a choice of six different office management systems from PC*CLAIM at $89.95 to Multi-User THRESHOLD® at $4990.00.

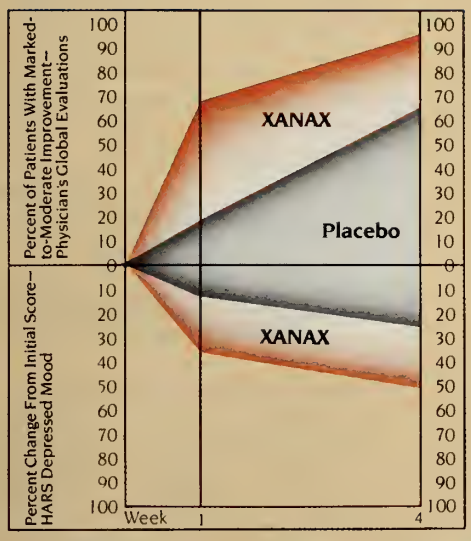
All PPM products run on any IBM®-PC™ or XT™, AT™ or PC-compatible. They're easy to operate because they use simple data entry methods. They're accurate because they use accepted insurance company codes. And they're cost-efficient because you get faster claims settlement and reimbursement. You can start off with the basics of PC*CLAIM and expand upwards without losing the work you've already invested. ☐ Take the paper and the pain out of filing insurance claims with PC*CLAIM or any of the office management systems from Physicians Practice Management, Inc. Specialists in automation for the medical profession.

Call toll free 1-800-428-2515. In Indiana call 1-800-792-2525

The CLAIM*NET nationwide clearinghouse is approved for live electronic claims submission to Medicare and other insurance companies in the following states: AL, AK, AZ, CA, CO, DE, FL, GA, HI, ID, IL, IN, IA, KY, LA, ME, MD, MA, MI, MN, MS, MO, NV, NH, NJ, NM, NY, NC, ND, OH, OK, OR, PA, SC, TN, TX, VT, VA, WA, DC, WI, WV, WY.


In 7 of 10
anxious
geriatrics...
Anxiety and
depressive
symptoms
go hand
in hand.

# Xanax effectively relieves anxiety with associated depressive symptoms.




In a recent clinical study[1] of 83 geriatric patients with clinical anxiety, 73% were diagnosed as having symptoms of depressed mood.

XANAX is well suited for therapy because it demonstrates greater efficacy than does placebo in reducing the Hamilton Anxiety Rating Scale Total Score and individual items, including depressed mood (see Figure).

# With clinical advantages for geriatric patients.

- Effectively relieves the symptoms of anxiety
- Also relieves anxiety with associated depressed mood
- Well tolerated—side effects, if they occur, are generally observed at the beginning of therapy and usually disappear with continued medication. Drowsiness and light-headedness were the most commonly reported adverse reactions
- Does not cause cardiovascular toxicity
- **Specific geriatric dosage**—0.25 mg, two or three times daily

1. Cohn JB. Double-blind safety and efficacy comparison of alprazolam and placebo in the treatment of anxiety in geriatric patients. *Curr Ther Res* 1984;35(1):100-112

**Xanax®** 0.25 mg Tablets
alprazolam C-IV

**Upjohn**

©1987 The Upjohn Company
Kalamazoo, Michigan 49001, USA

Please see adjacent page for brief summary of prescribing information

XANAX® Tablets
(alprazolam) ©

**CONTRAINDICATIONS**
Patients with sensitivity to this drug or other benzodiazepines and in acute narrow angle glaucoma.

**WARNINGS**
Not of value in psychotic patients. Caution patients against hazardous occupations requiring complete mental alertness and about the simultaneous ingestion of alcohol and other CNS depressant drugs.

Benzodiazepines can cause fetal harm in pregnant women. Warn patients of the potential hazard to the fetus. Avoid during the first trimester.

**PRECAUTIONS**
*General:* The dosage of XANAX Tablets should be reduced or withdrawn gradually, since withdrawal seizures have been reported upon abrupt withdrawal. If XANAX is combined with other psychotropics or anticonvulsant drugs, consider drug potentiation (see Drug Interaction section). Exercise the usual precautions regarding size of the prescription for depressed or suicidal patients. In elderly and debilitated patients, use the lowest possible dosage (see Dosage and Administration). Observe the usual precautions in treating patients with impaired renal or hepatic function.

***Information for Patients:*** Alert patients about: (a) consumption of alcohol and drugs, (b) possible fetal abnormalities, (c) operating machinery or driving, (d) not increasing dose of the drug due to risk of dependence, (e) not stopping the drug abruptly. *Laboratory Tests:* Not ordinarily required in otherwise healthy patients. *Drug Interactions:* Additive CNS depressant effects with other psychotropics, anticonvulsants, antihistamines, ethanol and other CNS depressants. Pharmacokinetic interactions with other drugs, e.g., cimetidine, have been reported. *Drug/Laboratory Test Interactions:* No consistent pattern for a drug or test. *Carcinogenesis, Mutagenesis, Impairment of Fertility:* No carcinogenic potential or impairment of fertility in rats. *Pregnancy:* See Warnings. *Nonteratogenic Effects:* The child born of a mother on benzodiazepines may be at some risk for withdrawal symptoms and neonatal flaccidity. *Labor and Delivery:* No established use. *Nursing Mothers:* Benzodiazepines are excreted in human milk. Women on XANAX should not nurse. *Pediatric Use:* Safety and effectiveness in children below the age of 18 have not been established.

**ADVERSE REACTIONS**
Side effects are generally observed at the beginning of therapy and usually disappear with continued medication. In the usual patient, the most frequent side effects are likely to be an extension of the pharmacologic activity of XANAX, e.g., drowsiness or lightheadedness.

*Central nervous system:* Drowsiness, lightheadedness, depression, headache, confusion, insomnia, nervousness, syncope, dizziness, akathisia, and tiredness/sleepiness. *Gastrointestinal:* Dry mouth, constipation, diarrhea, nausea/vomiting, and increased salivation. *Cardiovascular:* Tachycardia/palpitations, and hypotension. *Sensory:* Blurred vision. *Musculoskeletal:* Rigidity and tremor. *Cutaneous:* Dermatitis/allergy. *Other side effects:* Nasal congestion, weight gain, and weight loss.

Withdrawal seizures have been reported upon rapid decrease or abrupt discontinuation of XANAX. (See Precautions.)

In addition, the following adverse events have been reported with the use of benzodiazepines: dystonia, irritability, concentration difficulties, anorexia, transient amnesia or memory impairment, loss of coordination, fatigue, sedation, slurred speech, jaundice, musculoskeletal weakness, pruritus, diplopia, dysarthria, changes in libido, menstrual irregularities, incontinence and urinary retention.

Paradoxical reactions such as stimulation, agitation, increased muscle spasticity, sleep disturbances, and hallucinations may occur. Should these occur, discontinue the drug.

During prolonged treatment, periodic blood counts, urinalysis, and blood chemistry analysis are advisable. Minor EEG changes, of unknown significance, have been observed.

**DRUG ABUSE AND DEPENDENCE**
*Physical and Psychological Dependence:* Withdrawal symptoms have occurred following abrupt discontinuance of benzodiazepines. Withdrawal seizures have occurred upon rapid decrease or abrupt discontinuation of therapy. In all patients, dosage should be gradually tapered under close supervision. Patients with a history of seizures or epilepsy should not be abruptly withdrawn from XANAX. Addiction-prone individuals should be under careful surveillance. *Controlled Substance Class:* XANAX is a controlled substance and has been assigned to schedule IV.

**OVERDOSAGE**
Manifestations include somnolence, confusion, impaired coordination, diminished reflexes and coma. No delayed reactions have been reported.

**DOSAGE AND ADMINISTRATION**
Dosage should be individualized.

The usual starting dose is 0.25 to 0.5 mg, t.i.d. Maximum total daily dose is 4 mg. In the elderly or debilitated, the usual starting dose is 0.25 mg, two or three times daily. Reduce dosage gradually when terminating therapy, by no more than 0.5 milligram every three days.

**HOW SUPPLIED**
XANAX Tablets are available as 0.25 mg, 0.5 mg, and 1 mg tablets.

**Caution:** Federal law prohibits dispensing without prescription. B-5-S

**Upjohn** THE UPJOHN COMPANY
Kalamazoo, Michigan 49001 USA
1-7382
February 1987

## CONTINUING MEDICAL EDUCATION

*(Continued from Page 424)*

### CARDIOLOGY

April 27-May 6—**Cardiology for the Consultant.** Scripps Clinic and Research Foundation at Rancho Santa Fe Inn, Rancho Santa Fe. Mon-Wed. 40 hrs. $800. Contact: Bonny Mower, Dept of Academic Affairs, Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 457-8556.

May 1-2—**Arrhythmias: Interpretation, Diagnosis and Management.** Medical Education Resources at Bally's (MGM) Grand Hotel, Las Vegas, Nevada. Fri-Sat. 11 hrs. $295. Contact: Debbie Wilderson, Medical Education Resources, 5808 S Rapp St, Ste 202, Littleton, CO 80120. (800) 421-3756 or in CO 798-9682.

May 15-17—**Update in Cardiology/Resuscitation.** Superior California Medical Education Council, Redding at Alexander Valley (cycling tour). Fri-Sun. 6 hrs. Contact: J. Bear Co, PO Box 117, Burney 96013. (916) 335-3388.

May 24-30—**5th Annual Cardiology Update.** Institute for Medical Studies at Honolulu, Hawaii. Sun-Sat. 26 hrs. $395. Contact: Lisa Krehbiel, Inst for Med Studies, 30131 Town Ctr Dr, Ste 215, Laguna Niguel 92677. (714) 495-4499.

June 7-10—**Critical Examination Review Course.** American College of Chest Physicians at Hotel Del Coronado, Coronado. Sun-Wed. 30 hrs. $575. Contact: ACCP, PO Box 93826, Chicago, IL 60673. (312) 698-2200.

June 10—**Cardiology: Arrhythmias.** LLU at LLU. Wed. 4 hrs. $60. Contact: LLU.

June 10-13—**Advanced Echocardiography and Doppler Ultrasound—1987.** American College of Cardiology at Sheraton Harbor Island East, San Diego. Wed-Sat. Contact: Mary Anne McInerny, ACC, 9111 Old Georgetown Rd, Bethesda, MD 20814. (301) 897-5400, ext 226.

June 18-20—**Coronary Heart Disease: Current Concepts.** Medical Education Resources at Sheraton Waikiki Hotel, Honolulu, Hawaii. Thurs-Sat. 11 hrs. $295. Contact: Debbie Wilderson, Medical Education Resources, 5808 S Rapp St, Ste 202, Littleton, CO 80120. (800) 421-3756.

June 25-27—**Consultative Cardiology: Update in Diagnostic and Therapeutic Techniques.** American College of Cardiology at Westin South Coast Hotel, Costa Mesa. Thurs-Sat. Contact: Mary Anne McInerny, ACC, 9111 Old Georgetown Rd, Bethesda, MD 20814. (301) 897-5400, ext 226.

July 17-18—**Coronary Heart Disease: Current Concepts.** Medical Education Resources at Sheraton Hotel, Anaheim. Fri-Sat. 11 hrs. $295. Contact: Debbie Wilderson, 5808 S Rapp St, Ste 202, Littleton, CO 80120. (800) 421-3756.

July 31-August 1—**Arrhythmias: Interpretation, Diagnosis, and Management.** Medical Education Resources at Harvey's Hotel, Lake Tahoe, Nevada. Fri-Sat. 11 hrs. $295. Contact: Debbie Wilderson, 5808 S Rapp St, Ste 202, Littleton, CO 80120. (800) 421-3756.

August 2-7—**Current Concepts in Cardiology.** UCD at Hyatt Lake Tahoe, Incline Village, Nevada. Sun-Fri. Contact: UCD.

August 7-8—**Coronary Heart Disease: Current Concepts.** Medical Education Resources at Doubletree Inn, Monterey. Fri-Sat. 11 hrs. $295. Contact: Debbie Wilderson, 5808 S Rapp St, Ste 202, Littleton, CO 80120. (800) 421-3756 or (303) 798-9682.

### DERMATOLOGY

June 5-6—**6th Annual Southwestern Regional Cutaneous Flap Workshop.** UCLA at UCLA. Fri-Sat. 11 hrs. Contact: UCLA.

August 13-15—**Problems of the Aging Skin.** STAN at Hyatt Rickeys Hotel, Palo Alto. Thurs-Sat. Contact: STAN.

August 14-15—**Cryostat and Microscopically Controlled Surgical Workshop.** UCSD. Fri-Sat. 15 hrs. Contact: Daniel E. Gormley, MD, Director, 412 W Carroll, Glendora 91740. (818) 963-7684.

### EMERGENCY MEDICINE

April 24-26—**Advanced Cardiac Life Support.** CPR Seminars at Ralph K. Davies Medical Center, San Francisco. Fri-Sun. Contact: CPR Seminars, 833 Market St, Ste 421, San Francisco 94103. (415) 543-7282.

April 25-May 1—**Critical Care Medicine.** University of Colorado at Inter-Continental Hotel, Maui, Hawaii. Sat-Fri. 20 hrs. $395. Contact: Univ of CO, Office of CME, 4200 E 9th Ave, Box C-295, Denver, CO 80262. (303) 394-5195.

*(Continued on Page 429)*

CONTINUING MEDICAL EDUCATION

(Continued from Page 428)

May 4-8—**Postgraduate Institute for Emergency and Primary Care Physicians—Symposium I and Advanced Emergency Procedures Laboratory.** UCSD at Hotel Inter-Continental, San Diego. Mon-Fri. 32 hrs. $325-440. Contact: UCSD.

May 8-10—**Emergency Medicine Update.** Superior California Medical Education Council, Redding at Alexander Valley (cycling tour). Fri-Sun. 6 hrs. Contact: J. Bear Co, PO Box 117, Burney 96013. (916) 335-3388.

May 13-17—**9th Annual: Wound Management Workshop.** UCSD at San Diego Hilton Beach and Tennis Resort. Wed-Sun. Contact: Edith Bookstein, PO Box 2586, La Jolla 92038. (619) 454-3212.

May 15-17—**Update in Cardiology/Resuscitation.** Superior California Medical Education Council, Redding at Alexander Valley (cycling tour). Fri-Sun. 6 hrs. Contact: J. Bear Co, PO Box 117, Burney 96013. (916) 335-3388.

June 1-5—**Topics in Emergency Medicine.** UCSF at Holiday Inn Union Square, San Francisco. Mon-Fri. 31 hrs. $420. Contact: UCSF.

June 11-12—**Occupational and Environmental Medicine.** UCD at Capitol Plaza Holiday Inn, Sacramento. Thurs-Fri. 7 hrs. Contact: UCD.

June 22-26—**Postgraduate Institute for Emergency and Primary Care Physicians, Symposium III and Advanced Emergency Procedures Lab.** UCSD at Hanalei Hotel, San Diego. Mon-Fri. 32 hrs. $325-440. Contact: UCSD.

July 24-26—**Advanced Cardiac Life Support.** CPR Seminars at Ralph K. Davies Medical Center. San Franicsco. Fri-Sun. Contact: CPR Seminars, 833 Market St, Ste 421, San Francisco 94103. (415) 543-7282.

August 12-16—**Wilderness Medicine: 1987.** Siskiyou General Hospital at Northstar, Tahoe Resort. Wed-Sun. 20 hrs. $395. Contact: Jackie Silva, PO Box 321, Yreka 96097. (916) 842-6848.

August 17-21—**Postgraduate Institute for Emergency and Primary Care Physicians, Symposium II and Advanced Emergency Procedures Lab.** UCSD at UCSD. Mon-Fri. 32 hrs. $325-440. Contact: UCSD.

August 23-28—**New Advances in Internal Medicine.** UCD at Hyatt Monterey. Sun-Fri. Contact: UCD.

## INTERNAL MEDICINE

April 29—**Thyroid '87.** Hospital of the Good Samaritan at Moseley-Salvatori Conference Ctr, Los Angeles. Wed. 7 Hrs. Contact: Dolores Gay, Hosp of the Good Samaritan, 637 S Lucas Ave, Los Angeles 90017. (213) 977-2555.

May 2—**New Treatments in Liver and Biliary Tract Disease.** Scripps Clinic and Research Foundation, La Jolla. Sat. 7 hrs. $110. Contact: Bonny Mower, Dept of Academic Affairs, Scripps Clinic and Research Foundation, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 457-8556.

May 16—**Clinical Aspects of Viral Disease.** Grossmont District Hospital at Kona Kai Club, San Diego. Sat. Contact: Vera Belyeu, Grossmont District Hospital, 5555 Grossmont Center Dr, La Mesa 92041. (619) 465-0711, ext 245.

May 18-22—**Advances in Internal Medicine.** UCSF at Hyatt on Union Square, San Francisco. Mon-Fri. 32 hrs. $440. Contact: UCSF.

June 17-19—**Gastroenterology: Recent Developments in Theory and Practice.** UCSF at Hyatt on Union Square, San Francisco. Wed-Fri. 17 hrs. $375. Contact: UCSF.

June 22-26—**Advances in Internal Medicine.** UCSF at UCSF. Mon-Fri. 32 hrs. $440.

June 26—**Mucosal Injury, Esophageal Dysfunction, and Sleep Disorders.** Sequoia Hospital District, Redwood City. Fri. 7 hrs. $110. Contact: Daniel Liebowitz, MD, Sequoia Hospital, Whipple and Alameda, Redwood City 94062. (800) 345-0409.

## OB/GYN

April 30-May 2—**12th Annual Symposium: Care of the Sick Newborn.** UCI. Thurs-Sat. 19 hrs. Contact: UCI.

May 6-10—**Annual Scientific Program and Postgraduate Courses.** Pacific Coast Fertility Society at Americana Canyon Hotel, Palm Springs. Wed-Sun. 22 hrs. Contact: Pacific Coast Fertility Society, 5820 Wilshire Blvd, #500, Los Angeles 90036. (213) 937-5514.

May 7-8—**Advanced Fetal Rate Monitoring.** UCI. Thurs-Fri. Contact: UCI.

June 5-7—**OB/GYN: Antepartum and Intrapartum Management.** UCSF at Hyatt on Union Square, San Francisco. Fri-Sun. 18 hrs. $200-320. Contact: UCSF.

June 11-13—**Gynecologic Oncology and Breast Disease.** American College of Obstetricians and Gynecologists at Fairmont Hotel, San Francisco. Thurs-Sat. Contact: Robin Murray, ACOG, 600 Maryland Ave, SW, Washington, DC 20024-2588. (202) 638-5577.

June 30-July 5—**5th Annual Controversies in Obstetrics and Gynecology.** UCI at Mauna Kea Beach Resort, Hawaii. Tues-Sun. 22 hrs. Contact: UCI.

## OPHTHALMOLOGY

August 1-8—**Ophthalmology.** USC at Mauna Kea, Hawaii. One week. 26 hrs. $525. Contact: USC.

## ORTHOPEDICS

April 30-May 2—**American Back Society Spring Symposium on Back Pain.** Anaheim Hilton Hotel. Thurs-Sat. Contact: Aubrey A. Swartz, MD, American Back Society, 2647 E 14th St, Oakland 94601. (415) 536-9929.

May 2-3—**Automated Percutaneous Lumbar Discectomy Workshop.** UCSF at Hyatt Regency, San Francisco. Sat-Sun. Contact: UCSF.

May 4-6—**Osteoporosis Update—1987.** UCSF at Hyatt Regency, San Francisco. Mon-Wed. 18 hrs. $295. Contact: UCSF.

May 6-8—**Spine Update—1987.** UCSF at Hyatt on Union Square, San Francisco. Wed-Fri. 17 hrs. $295. Contact: UCSF.

June 14-19—**Fingers to the Toes: Orthopaedics for Primary Care.** UCD at Stanford Sierra Camp, Fallen Leaf Lake. Sun-Fri. Contact: UCD.

## PATHOLOGY

May 21-22—**Annual Meeting: Current Issues in Anatomic Pathology.** UCSF at San Francisco. Thurs-Fri. 12 hrs. Contact: UCSF.

August 22-29—**7th Annual Symposium on Fine Needle Aspiration.** California Society of Pathologists and UCSF at Royal Lahaina Resort, Kaanapali Beach, Maui, Hawaii. One week. 24.5 hrs. Contact: UCSF.

## PEDIATRICS

May 2-9—**Forefronts in Pediatrics.** EPIC Expeditions and University of Arizona at Sonoma and Napa Valleys. One week. 24 hrs. Contact: Kathy Rairigh, EPIC Expeditions, PO Box 209, Sun Valley, ID 83353. (208) 788-4995.

May 4-7—**Pediatrics in the 80s—The 17th Annual Pediatrics Course.** USC at Marina Beach Hotel, Marina del Rey. Mon-Thurs. 18.5 hrs. $395. Contact: USC—in California, (800) 321-1929, National, (800) 421-6729.

May 21-23—**American Academy of Pediatrics Spring Session.** AAP at San Francisco. Thurs-Sat. Contact: Guy Di Cara, AAP, PO Box 927, Elk Grove Village, IL 60007. (800) 433-9016, or in Illinois, (800) 421-0589.

July 24-25—**Debates and Updates in Pediatric Emergencies.** UCSF at Hyatt on Union Square, San Francisco. Fri-Sat. 14 hrs. $235. Contact: UCSF.

## RADIOLOGY

April 19-24—**7th Annual San Diego Residents' Radiology Review Course.** UCSD at Town and Country Hotel, San Diego. Sun-Fri. 39 hrs. $395. Contact: UCSD.

May 1-3—**12 Annual Spring Diagnostic Ultrasound.** Los Angeles Radiological Society at Century Plaza Hotel, Los Angeles. Fri-Sun. 19.5 hrs. $325. Contact: Diane L. Johnson, LARS, 5200 Century Blvd, Ste 920, Los Angeles 90045. (213) 642-0921.

(Continued on Page 509)

# A better alternative for hypertensives who are going bananas...

*Spare your patients the extra cost—in calories, sodium and dollars.*

*Spare your patients the rigors of dietary $K^+$ supplementation.*

# DYAZIDE®

**25mg** Hydrochlorothiazide/**50mg** Triamterene/SKF

## Effective antihypertensive* therapy...without the bananas

* Not for initial therapy. See brief summary.

**Before prescribing, see complete prescribing information in SK&F CO. literature or PDR. The following is a brief summary.**

* **WARNING**

This drug is not indicated for initial therapy of edema or hypertension. Edema or hypertension requires therapy titrated to the individual. If this combination represents the dosage so determined, its use may be more convenient in patient management. Treatment of hypertension and edema is not static, but must be reevaluated as conditions in each patient warrant.

**Contraindications:** Concomitant use with other potassium-sparing agents such as spironolactone or amiloride. Further use in anuria, progressive renal or hepatic dysfunction, hyperkalemia. Pre-existing elevated serum potassium. Hypersensitivity to either component or other sulfonamide-derived drugs.

**Warnings: Do not use potassium supplements, dietary or otherwise, unless hypokalemia develops or dietary intake of potassium is markedly impaired.** If supplementary potassium is needed, potassium tablets should not be used. Hyperkalemia can occur, and has been associated with cardiac irregularities. It is more likely in the severely ill, with urine volume less than one liter/day, the elderly and diabetics with suspected or confirmed renal insufficiency. Periodically, serum $K^+$ levels should be determined. If hyperkalemia develops, substitute a thiazide alone, restrict $K^+$ intake. **Associated widened QRS complex or arrhythmia requires prompt additional therapy.** Thiazides cross the placental barrier and appear in cord blood. Use in pregnancy requires weighing anticipated benefits against possible hazards, including fetal or neonatal jaundice, thrombocytopenia, other adverse reactions seen in adults. Thiazides appear and triamterene may appear in breast milk. If their use is essential, the patient should stop nursing. Adequate information on use in children is not available. Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma. Possible exacerbation or activation of systemic lupus erythematosus has been reported with thiazide diuretics.

**Precautions:** The bioavailability of the hydrochlorothiazide component of 'Dyazide' is about 50% of the bioavailability of the single entity. Theoretically, a patient transferred from the single entities of triamterene and hydrochlorothiazide may show an increase in blood pressure or fluid retention. Similarly, it is also possible that the lesser hydrochlorothiazide bioavailability could lead to increased serum potassium levels. However, extensive clinical experience with 'Dyazide' suggests that these conditions have not been commonly observed in clinical practice. Angiotensin-converting enzyme (ACE) inhibitors can elevate serum potassium; use with caution with 'Dyazide'. Do periodic serum electrolyte determinations (particularly important in patients vomiting excessively or receiving parenteral fluids, and during concurrent use with amphotericin B or corticosteroids or corticotropin [ACTH]). Periodic BUN and serum creatinine determinations should be made, especially in the elderly, diabetics or those with suspected or confirmed renal insufficiency. Cumulative effects of the drug may develop in patients with impaired renal function. Thiazides should be used with caution in patients with impaired hepatic function. They can precipitate coma in patients with severe liver disease. Observe regularly for possible blood dyscrasias, liver damage, other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving triamterene, and leukopenia, thrombocytopenia, agranulocytosis, and aplastic and hemolytic anemia have been reported with thiazides. Thiazides may cause manifestation of latent diabetes mellitus. The effects of oral anticoagulants may be decreased when used concurrently with hydrochlorothiazide; dosage adjustments may be necessary. Clinically insignificant reductions in arterial responsiveness to norepinephrine have been reported. Thiazides have also been shown to increase the paralyzing effect of nondepolarizing muscle relaxants such as tubocurarine. Triamterene is a weak folic acid antagonist. Do periodic blood studies in cirrhotics with splenomegaly. Antihypertensive effects may be enhanced in post-sympathectomy patients. Use cautiously in surgical patients. Triamterene has been found in renal stones in association with the other usual calculus components. Therefore, 'Dyazide' should be used with caution in patients with histories of stone formation. A few occurrences of acute renal failure have been reported in patients on 'Dyazide' when treated with indomethacin. Therefore, caution is advised in administering nonsteroidal anti-inflammatory agents with 'Dyazide'. The following may occur: transient elevated BUN or creatinine or both, hyperglycemia and glycosuria (diabetic insulin requirements may be altered), hyperuricemia and gout, digitalis intoxication (in hypokalemia), decreasing alkali reserve with possible metabolic acidosis. 'Dyazide' interferes with fluorescent measurement of quinidine. Hypokalemia is uncommon with 'Dyazide', but should it develop, corrective measures should be taken such as potassium supplementation or increased dietary intake of potassium-rich foods. Corrective measures should be instituted cautiously and serum potassium levels determined. Discontinue corrective measures and 'Dyazide' should laboratory values reveal elevated serum potassium. Chloride deficit may occur as well as dilutional hyponatremia. Concurrent use with chlorpropamide may increase the risk of severe hyponatremia. Serum PBI levels may decrease without signs of thyroid disturbance. Calcium excretion is decreased by thiazides. 'Dyazide' should be withdrawn before conducting tests for parathyroid function. Thiazides may add to or potentiate the action of other antihypertensive drugs. Diuretics reduce renal clearance of lithium and increase the risk of lithium toxicity.

**Adverse Reactions:** Muscle cramps, weakness, dizziness, headache, dry mouth; anaphylaxis, rash, urticaria, photosensitivity, purpura, other dermatological conditions; nausea and vomiting, diarrhea, constipation, other gastrointestinal disturbances; postural hypotension (may be aggravated by alcohol, barbiturates, or narcotics). Necrotizing vasculitis, paresthesias, icterus, pancreatitis, xanthopsia and respiratory distress including pneumonitis and pulmonary edema, transient blurred vision, sialadenitis, and vertigo have occurred with thiazides alone. Triamterene has been found in renal stones in association with other usual calculus components. Rare incidents of acute interstitial nephritis have been reported. Impotence has been reported in a few patients on 'Dyazide', although a causal relationship has not been established.

**Supplied: 'Dyazide' is supplied as a red and white capsule, in bottles of 1000 capsules; Single Unit Packages (unit-dose) of 100 (intended for institutional use only); in Patient-Pak™ unit-of-use bottles of 100.**

BRS-DZ:L42

a product of
**SK&F CO.**
Carolina, P.R. 00630

© SK&F Co., 1986

Marshall B. Block, M.D.

ARIZONA MEDICINE

JOURNAL OF ARIZONA MEDICAL ASSOCIATION

APRIL 1987, VOL. XLIV, NO. 4

# The Role of the Media In Reporting Medical News

The media, electronic and print, needs to gain the public's attention in order to sell its goods. It therefore tends to sensationalize information in order to reach its respective audiences. Sometimes the sensationalism goes too far and although the media tends to be generally responsible, it can present, on occasion, an unbalanced viewpoint to its constituents. Medicine and health-related matters are of major interest to the public, and anytime new breakthroughs occur, the media tends to give wide exposure to such occurrences. Over the past years, several inconsistencies in the media's reporting of medical events prompts me to write this editorial.

In the past, one of our local newspapers, *The Scottsdale Progress,* was extremely inconsistent in its editorial policy regarding the building of a peripheral hospital in one of the expanding outlying northern communities. An initial editorial supported the development of the hospital. It subsequently wrote an additional editorial condemning the hospital board for building the hospital in that location once the extremely low occupancy rate was apparent and hospital system rates had to be increased to cover the loss suffered by this new hospital. The editorial board in that situation was unfair to its readers, but more importantly was not responsible in its position. A more thoughtful balanced approach in its editorial policy would have presented both sides of the story initially and allowed the community to reach its own decisions before the hospital was built.

Pancreatic transplantation gained wide publicity when several patients in the Valley underwent this experimental procedure. The one-sided presentation of "a breakthrough" on TV and the *Arizona Republic* gave false hope to patients with the disorder, and I think it did more disservice than good to its constituents. Rather than obtaining information from others not intimately involved with the transplantation process as to the possible adverse side effects and longterm viability of such transplants, the media chose to just present the positive upbeat side of the story.

The media and the medical profession have an uncomfortable relationship. The media needs the medical profession for its expertise, but at the same time distrusts to some extent the medical profession because of its possible bias in presenting the scientific information. The media embroils itself in controversial issues without really knowing the players or the powers. Many times in the process the media gets polarized and does not present a balanced position. I think the media in its attempt to generate headlines sometimes doesn't do its homework to the extent necessary to fully understand the issues involved. Responsible journalism requires responsible reporters and editors who demand to know the whole story, not just a portion. Consistency by the editorial board, whether it be a newspaper or a television station, is essential for the well-being of the community in which it purports to serve. Rather than give itself awards for electronic and printed excellence, the information media should be judged by outside forces which make the news and perhaps have a better understanding of the complexity of the issues involved. "Letters to the editors," the subsequent retractions and caveats do not balance the big headlines and bold type or verbal hype that precede many of these sensational stories. Perhaps an outside panel composed of consumer advocates, medical, legal and other professionals in various walks of life, should be judging the media's presentation. ■

**Marshall B. Block, M.D., Editor**

*Arizona Medicine* is published monthly by the Arizona Medical Association, Inc. • 810 West Bethany Home Road • Phoenix, Arizona 85013 • (602) 246-8901.

# MICA

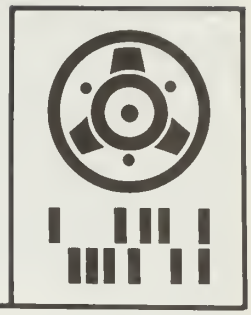
## IN ITS SECOND DECADE
## OF PROVIDING QUALITY
## MEDICAL MALPRACTICE INSURANCE

## LIMITED TO ARIZONA PHYSICIANS
## WHO ARE PREFERRED RISKS

For more facts, please call the MICA Underwriting
Department (602) 956-5276
or toll free (800) 352-0402

MICA MICA MICA MICA MICA

MUTUAL INSURANCE COMPANY OF ARIZONA Sponsored by: Arizona Medical Association
Arizona Osteopathic Medical Association



# Nationwide Network Provides Single-Entry Point for Electronic Claims

A new way to submit claims electronically is now available to physicians in Arizona. Technology developed by General Electric Information Service Company will enable medical office systems to routinely dial a telecommunications network and submit claims to over thirty carriers, including Aetna Life And Casualty Company (Medicare 'B' claims) and to The National Electronic Information Corporation, (NEIC) for commercial carrier and Railroad Retirement claims.

The claims clearinghouse network is available by a local call from 3 cities in Arizona and a total of 650 cities nationwide. There is a toll free number for practices outside the local dial areas.

Designated the EMC*EXPRESS™ System, the service has been introduced successfully in Illinois, Southern California and Pennsylvania. GE Information Services is marketing the service by working with over 40 vendors of physician and hospital computer and software systems. The Company and the vendor select and tailor appropriate communication technologies. These vendors then aid medical offices in switching from papers claims to paperless claims systems.

In place, the system works something like this:

A typical subscriber might be a physician with a microcomputer and a practice management software package. During the day, the system is used to maintain patient records, prepare financial reports and provide word processing capability. As patient claims are prepared on the computer, they are stored for batch transmission that night. At the appropriate time the computer dials the local telephone number of the GE teleprocessing network and transmits the claims accumulated during the practice day.

Claims are sorted by a central computer and stored in "mailboxes" to await a phone call from the designated insurance carrier. Carriers call after 3:00 AM each day and extract the claims. Thus, claims can be resident in the carrier's computer within 24 hours of the patient visit. Error reports are returned electronically by some carriers.

Some vendors also offer microcomputers which function strictly as claims entry workstations.

The benefits to physicians are:

- Faster turnaround of claims — By eliminating mail delays and claims entry work at the carrier site, a significant number of days can be cut from the process.
- Lower error rates — Computer systems are capable of checking for designated errors and omissions before the claim is sent and normally reduce or eliminate the need to manually reenter data — the process which is most susceptible to human error.
- Reduced administration costs — Software vendors' systems send claims to EMC*EXPRESS in unattended mode, after normal business hours, thus reducing practice administrative costs.

The network supports a wide variety of devices and protocols from either the provider side or the carrier side. This means that subscribers to the clearinghouse generally can continue to use existing computer equipment and avoid the need to invest in new equipment, other than a commumications modem.

In effect, the GE network is acting as a single pipeline to the primary carriers accepting

batches of claims from a number of health care providers and preparing them for pickup by insurance carriers.

As a result, it is possible for physicians and billing services to access the network and to submit claims in one format to the local Medicare Part B carrier, Medicaid, Railroad Retirement, and to processors of group health claims, including Blue Shield.

A list of participating carriers is shown in the accompanying table.

**NEIC Active Participants**
Aetna Life and Casualty (Medicare A, B, and Commercial)
Allstate Life Insurance Company
Principal Mutual Financial Group
Benefit Trust Life Insurance Company
CNA Insurance Companies
Confederation Life Insurance Company
Connecticut General Life Insurance Company
Equitable Life Assurance Society of the U.S.
The Great-West Life Insurance Company
Gulf Group Services
The Hartford Insurance Group
Home Life Insurance Company
John Hancock Mutual Life Insurance Company
Liberty Life Assurance Company
Lincoln National Life Insurance Company
Massachusetts Mutual Life Insurance Company
Metropolitan Life Insurance Company
Mutual of Omaha Insurance Company
New England Mutual Life Insurance Company
New York Life Insurance Company
Pacific Mutual Life Insurance Company
Philadelphia American Life Insurance Company
Phoenix Mutual Life Insurance Company
Pilot Life Insurance Company
Provident Life & Accident Insurance Company
Prudential Insurance Company (Commercial and Medicare 'B')
State Mutual Life Assurance Company of America
The Travelers Insurance Company
(Including Medicare 'B' and Railroad Retirement)
Unionmutual Stock Life Insurance Company

**Other Commercials**
Transamerica Occidental Life

Ronald J. Meyer, Manager
Insurance Industry Marketing

SEA

**S.E.A., Inc.**
2050 E. 5th St.
Tempe, AZ 85281

**Quality Microscopes and Medical Equipment**

We sell Parco & Swift & aus Jena Microscopes. We also handle Miltex Surgical Instruments, Bio-Dynamics Equipment, B/P Cups, Stethoscopes, Beiersdorf Products, as well as many other Medical Products.

**25 Years Experience**

**We Service and Repair All Types of Microscopes**

**(602) 258-8368**
**(602) 966-2417**

**FAST GROWING Nation-Wide Franchise**

Sale and Delivery of Teddy Bears
ALL OCCASIONS

For Sale: Mesa Store & Franchise

PERFECT for: Family, 2nd Income or Woman's Start-up Business

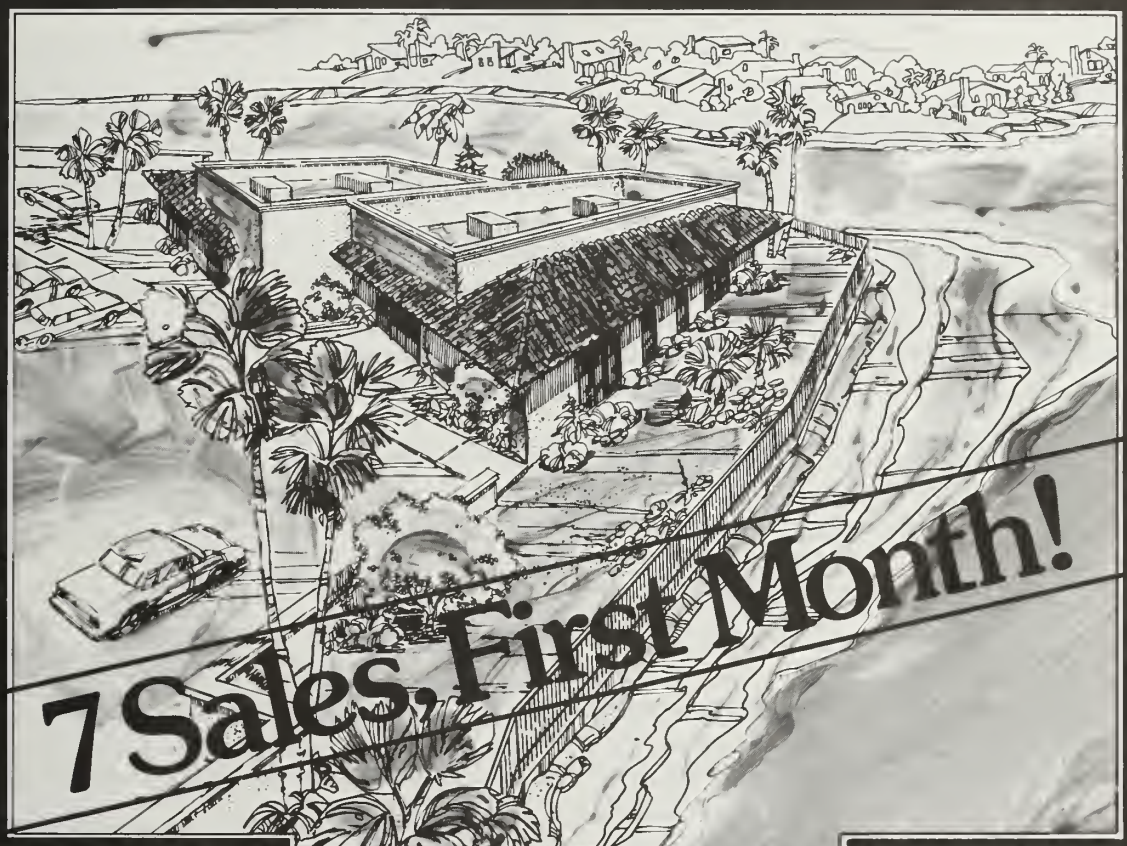
Call owner evenings
(712) 225-2131
Estimated Investment — $50,000

AN OUTSTANDING LOCATION □ A REMARKABLE VALUE

# *Bank Sale Presents A Unique Opportunity.*

Practice at a premium location on the shore of Dobson Ranch Lake, part of the Dobson Ranch planned community. Located just south of the Dobson Road and Baseline intersection, a short drive from Desert Samaritan and five other East Valley Hospitals.

Enjoy the tax benefits of an owner-occupied medical office that features easy freeway access, open space, individually signed identity, ample parking at your door and street level entry with in-and-out ease for handicapped patients. Choose from eighteen separate units in seven building clusters.




## Dobson Ranch Professional Center

2058 South Dobson Road □ Mesa, Arizona

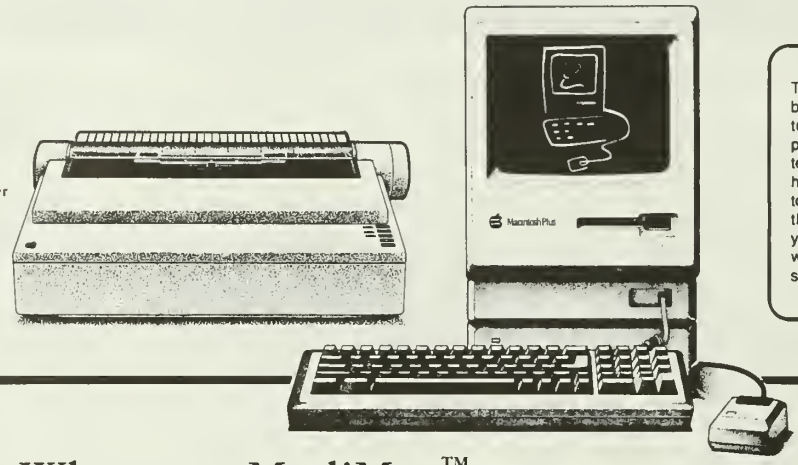
Managed and Marketed by
**Lowe Associates, Inc.**

Contact your local Broker or Telephone Peter Koenig, 279-0120

# MediMac™

## The incredible medical information management system for the Apple Macintosh.™

Authorized Dealer



The Macintosh™ Plus Computer combines powerful technology with an intuitive way of working, enabling you to put it to work right away. The large internal memory, processing power, and high-capacity disk drives of the Macintosh™ Plus help you get through even the biggest jobs fast. You can expand your Macintosh™ Plus system with a wide variety of high speed peripherals, such as hard-disk drives.

## What can MediMac™ mean to your practice?

Suppose at the push of a button you could produce an insurance form ready for the patient to sign and ready for you to mail.....and in a matter of minutes, you could communicate with every patient you are currently treating.....and without a laborious search of your files, you could routinely acknowledge all patient referrals.....AND THE BEST PART IS....YOU DON'T HAVE TO BE A COMPUTER EXPERT TO USE IT!!!!!

## SOME OF THE FEATURES

- Production Summary by Physician — Provides production information for each physician in summary format.
- Production Detail by Physician — Provides individual CPT activity summaries by fee schedule.
- Daily Production by Physician - Summarizes each day's activities and provides a running A/R balance.
- Receipts by Physician - Lists amounts collected.
- Patient Statements - Provides statements in flexible formats, with or without interest charges.
- Batch Printing of Insurance Forms - Produces batch insurance claim forms for any selected insurance plan.
- Aging Analysis - An alphabetically ordered printout of every unpaid balance, the amount due and days overdue, or totals only.
- Patient Follow Up — Lists all patients due back for office visits.
- Inactive Patients — Lists patient's date of last visit and balance due.
- Marketing Reports — Including Patients by Birthdates, Referrals (by and to), Recall, Collections.
- Management Reports — Including Work to be Completed, Inactive Patients, Patients, with Credit Balances, Patients on Installment Plans.
- Provides immediate access to individual patient files, family information, employer/insurance information, to help you serve your patients more efficiently.
- Allows "windowing" so multiple patients can be displayed at one time.
- Records complete information on all patient transactions, including physician, diagnosis, procedures performed and fees.
- Allows flexibility in determining information to be included in patient billing.
- Prints statements, insurance claim forms, patient lists and summaries, mailing and chart labels, and more.
- Produces completed claim forms for up to 1,000 different insurance plans.
- Stores 2,500 diagnostic codes and up to 50 different fee schedules.

***Call us for additional information and a Hands-On-Demonstration.***

**E. CAMELBACK RD.**
914 E. Camelback Road
285-0985

**PARADISE VALLEY**
Village Square Center
4621 E Cactus Rd
953-1884

**COMPUSHARE**
**PERSONAL COMPUTER CENTERS**
SALES • TIME SHARING • EDUCATION • SERVICE

**METROCENTER**
Metro Village Center
2851 W. Peoria,
943-4858

**MESA**
Poca Fiesta Center
1110 W Southern
898-0610

Apple and the Apple logo are registered trademarks of Apple Computer, Inc
Macintosh is a trademark of McIntosh Laboratory, Inc. and is being used with express permission of its owner.
**MediMac is a trademark of HealthCare Communications, Inc.**

# Mental Pain

When physical pain becomes unbearable, nature simply closes the curtains of consciousness. No such natural relief or escape has yet evolved in cases of mental suffering. This is why suicide is more prevalent in so-called functional disorders than in those due to demonstrable organic disease. And any level of oblivion induced by alcohol or other drugs is patently a partial suicide.

As blood chemistries become more sophisticated, the kinds and degrees of mental suffering may soon be measurable. We already have laboratory tests for certain types of depression. Sources of psychic pain, however, have not even been classified. A few will be mentioned.

1. *Inhospitality.* Through no fault of their own, some individuals and groups are made to feel unwelcome in their worlds.

Perhaps Christian theologians should reconsider the whole concept of original sin. Guilty and damned unless redeemed? It sounds unconstitutional—but the subject is outside our expertise.

In everyday life we view—or avert our gaze from—widespread bigotry and prejudice. Note the word, prejudice, pre-judging. How quick we are to jump to harshly biased opinions! How ready we are to gossip and to make snide remarks about our friends!

Urban crowding is a key to anonymity, and this in turn opens cages of rudeness and insensitivity. In traffic we are developing into hard-shelled beetles, mindlessly rushing and aggressive. Away from home and among strangers one's reputation is not exposed and not at risk. A visitor to the city can go heedlessly to a porno movie or a gay bar. An "anonymous source" can be a liar with impunity.

Nameless is blameless!

Big town anonymity, by the way, can be seen as a significant element in the apparent breakdown of morality, which is in fact a breakdown in the consequences of immorality.

Just as wearying as outright rejection is questionable welcome—which is not welcome at all! Witness the groveling of the puppy until we signal some greeting. Or recognize the ingratiating little smile with which a person approaches an intimidating bureaucrat or boss or landlord. The uncertain smile is a weakly magical request for responsive cordiality and warmth.

A severe case of anorexia began when dormitory mates neglected to include a shy newcomer on their merry way to the school cafeteria. Ostracisms, whether intentional or not, are quite common in the workplace. Friendlessness can be fatal; and unkindness is as culpable as any other homicide.

2. *Unattractiveness.* Physical deformity, obesity or plain ugliness can bring on riducule and mockery, and the victim has no defense. A more tragic affliction is the unattractive personality. In order to survive in a murky environment, a growing individual will have had to develop defensive traits, and these traits may later prove abrasive or repellant. If we would take pains to understand a person's background we could see why he became so suspicious or secretive or overcompensating or histrionic or seemingly helpless. Popular psychology has failed to convey how very hard it is to know someone and hence to make allowances. It is a desolate fact that I can never walk that mile in your moccasins, nor you in mine.

3. *Incompetence.* One of the most malignant sources of mental suffering is incompetence. Unrelenting strain is the curse of any individual who cannot quite measure up to the demands of his job or expectations implicit in one or another of his roles.

The battered child is the one who is a constant reminder of the parent's inadequacy, and so with the bullied spouse.

A surgeon developed a rhythmic head tremor. It was side-to-side, like a negation, and there was no neurologic basis. He had served a kind of apprenticeship in association with a better trained and more talented colleague. With the untimely death of his mentor the young man had to brace himself against a surf of responsibilities with which he wasn't prepared to cope.

The riotings of the sixties ought to alert us to be wary of pushing advantages toward people who are ill-equipped and can't stand to be reminded of the fact. By the same token we hesitate to endorse permissiveness in the rearing of children, lest they spend their lives paying for our misguided indulgence. In the impersonal and unforgiving world of adults it is too late to learn diligence or frustration tolerance or the importance of appearance (what else can we

judge by?) and good manners.

4. *Aimlessness.* Longevity is by no means an unalloyed blessing. A successful individual, especially a member of a profession, will have thrived on a diet rich in recognition. In retirement such is an unacceptable loss.

Again, without intending to devaluate religion, we have to complain about the carrot-on-stick notion in both Eastern and Western systems; namely, that full comprehension and the balancing of the books will not take place until some future life. Aside from scripture-based religions there just isn't any satisfactory philosophy in our times, and this is a worldwide famine. Atheism and humanism seem empty and tell us little or nothing about our place and purpose in this awesome universe.

To live without significant purpose is boring and bleak. Assembly line technology seems to be turning us into robots, without souls or substance. Have you noticed how retired couples put up fences against any disruption of their petty routines? Only the participants are fooled by the sham enthusiasms and gaiety of retirement communities with their toothy bicycle riding and their hobby shops and dancing lessons. Young people in the cabs of their pickup trucks deaden their minds and their acoustic nerves with screaming radios. Meanwhile we are watching television, sparing ourselves from talking to each other because there is nothing to say.

5. *Addiction.* Any addiction, especially alcoholism, is very depressing. Alcohol or the drug soon becomes a drying substitute for instinctual gratifications and for estimable accomplishments and healty recreations. In narrowing circles the addict's life revolves around maintaining his supply and avoiding withdrawl, and so he becomes self-centered. No substance would be addictive if it were not poisonous. The addict, then, will never be without dread, cringing in anticipation of physical and social disaster, alienated from friendship and from sympathy and forgiveness, even from himself.

6. *Bereavement.* Grief is almost always a dual suffering. One is hurt by the loss of something or someone beloved. One is doubly hurt by the loss of the identity he had in the reciprocal relationship.

In this respect grief is not unlike phantom pain. Following amputation, one's body and mind must struggle to revise one's inner image of himself, and this is an angry and unwilling task.

Death of a husband, for example, rends the fine garments of his surviving spouse. She may feel self-conscious, almost ashamed, as if half-dressed, while she changes to her widow's weeds. Earlier we mentioned the successful man and the recognitions he gets, and we used the word on purpose. With retirement he, too, will be symbolically almost naked. He may then manifest uncharacteristic traits of unobtrusiveness and diffidence, and he will have phantom pains.

7. *Chagrin.* This is surely the most miserable of mental sufferings. Once in a blue moon even the steadiest of us has done something inexcusably wrong and stupid. And got caught! On a flight from Hawaii, during one of those times when I was supposed to have quit smoking, I pilfered a cigarette from an open pack in the flight attendants' area. The self-righteous stewardess wouldn't make light of the offense or be a good sport about it. I have never forgotten my defenseless humiliation. And I have wondered about the chemistry—sick as a pup that has bitten into the head gland of a toad.

Mortification is a kind of gangrene of the spirit. When adolescent lust or infantile temper tricks an individual into a shameful situation, his special suffering is compounded by the fact that he cannot portray himself as a victim of circumstances or blame anyone except himself. And this in turn forfeits the sympathetic fellowship which lightens other burdens by sharing them.

Mental suffering can be far more devastating than physical pain. This is made graphic when an individual, angry at himself or overwhelmed by grief, will hit a wall with his fist or bite the back of his hand. Similar mechanisms of conversion or displacement are engaged more chronically and unconsciously in neuroses and in some of the psychosomatic disorders.

The mind is infinitely complicated. In cases of mental suffering the standard expression of sympathy, "I know what you're going through," is inappropriate, untrue and not entirely welcome. And neither is unsolicited advice! Our most grateful friends or patients have often been those with whom we have felt ineffectual because we could not think of anything helpful to suggest. The wisest help is just to be there and be quiet and listen. ■

William B. McGrath, M.D.

AIM HIGH

# A PRESCRIPTION FOR PHYSICIANS

**BOTHERED BY:**

- ★ Too much paperwork?
- ★ The burden of office overhead?
- ★ Malpractice insurance costs?
- ★ Not enough time for the family?
- ★ No time to keep current with technology and new methods?
- ★ No time or money for professional development?

**JOIN THE AIR FORCE MEDICAL TEAM; WE'LL PROVIDE THE FOLLOWING:**

- ★ Competent and dedicated professional staff.
- ★ Time for patients and for keeping professionally current.
- ★ Financial security, a generous retirement for those who qualify.
- ★ If qualified, unlimited professional development.
- ★ Medical facilities all around the world.
- ★ 30 days of vacation with pay each year.
- ★ Complete medical and dental care.
- ★ Low cost life insurance.

Want to find out more? Contact your nearest Air Force recruiter for information at no obligation. Call

AIR FORCE

# Medical Director
## Phoenix Health Plan

Phoenix Health Plan, an AHCCCS provider, part of Phoenix Memorial Hospital Primary Care, Inc., is currently seeking a full-time Medical Director. Arizona licensure is required with Board Certification in a primary care specialty preferred. Responsibilities include development of utilization control, sight review protocols and claims review procedures. Experience in pre-paid medicine, quality assurance, utilization control and administration/management is required.

Please send resume to: **Human Resources Dept. (PH-PMH), Phoenix Memorial Hospital, 1201 S. 7th Ave., Phoenix, AZ 85007.** Equal Opportunity Employer.

PHOENIX MEMORIAL HOSPITAL
People Matter Here

**TAX & PENSION**

**DESIGNED**

**REAL ESTATE FINANCING**

Residential Refinancing
New Purchases
Small Medical Office Buildings

*LOW RATES — MINIMAL POINTS*

No Charge To You For
Tax Designed
And
Pension Oriented
Mortgages

**MARVIN H. BENDAU**
**MORTGAGE BROKER**
**943-7229**

PHOENIX MANAGEMENT SERVICES INC.

# PMS THE Collectors

SINCE 1980

FOR

**MEDICAL • RETAIL • COMMERCIAL**

LICENSED • BONDED
FAST • COURTEOUS • PROFESSIONAL
NATIONAL & INTERNATIONAL COLLECTIONS

**CALL THE PROFESSIONALS**
3530 E. INDIAN SCHOOL RD.

# 956-3459

# Physicians in the News . . .

**Neopito L. Robles, M.D.** above right, Tucson surgeon and ArMA delegate to the American Medical Association House of Delegates, receives congratulations from AMA speaker of the House **James E. Davis, M.D.** Dr. Robles was one of 26 physicians honored during the recent gathering of the House of Delegates in Las Vegas for outstanding achievement in AMA membership recruitment. Dr. Robles recruited nine new AMA members and was awarded the special AMA blazer with the official emblem of the House of Delegates Physician Outreach Program. Celebrating with Dr. Robles, below, are from left, **Doris and Joseph S. Whaley, M.D.**, of Tucson; **John J. Coury, M.D.**, President of the American Medical Association; **Dr. Robles**; and **Bette and Jack M. Layton, M.D.**, of Tucson.

## SMHSI Founding Member Retires

**Arthur D. Nelson, M.D.**, announced his retirement from Scottsdale Memorial Health Systems, Inc. (SMHSI) at the January meeting of the SMHSI Board of Directors. The board honored Dr. Nelson by designating him president of the System.

Dr. Nelson, a founding member of the Scottsdale Memorial Health Foundation Board of Directors, joined Scottsdale Memorial as director of the Family Practice Residency Program in 1974. He was named president of the hospital in 1976 and president and chief executive officer of SMHSI in 1981. In 1985, he was named chairman of the SMHSI Board of Directors Executive Committee.

At the board's request, Dr. Nelson agreed to be available to assist the hospitals in future planning and development. He will remain as a member of the board of directors of SMHSI and as a trustee of the Foundation.

Dr. Nelson is a graduate of the U.S. Military Academy at West Point and Temple University School of Medicine, and holds a masters degree in civil engineering from Harvard University.

He has been a consultant for the Department of Health, Education and Welfare; an adjunct professor for the University of Arizona's Department of Community Medicine and Family practice; and a member of the board of directors of the Scottsdale Chamber of Commerce. He is currently a member of the board of directors of the Scottsdale Symphony, the Harvard Business School Club of Arizona, and the Greater Phoenix Affordable Health Care Foundation.

Dr. Nelson and his wife, Linda Brock-Nelson, live in Paradise Valley.

**Jane M. Orient**, M.D., a solo internal medicine specialist from Tucson, has become the first woman elected president of the Association of American Physicians and Surgeons. (AAPS)

Dr. Orient joined AAPS soon after going into private practice in Tucson in 1981, became a member of the AAPS Board of Directors and served as its vice president during the 1985-86 fiscal year.

She said her goals for her presidency include leading AAPS to oppose Congressional legislation and other governmental intrusion into the practice of private medicine and to bolster membership of the organization. The 2,000-member AAPS was founded in 1943 to promote the private practice of medicine and to supplement the professional scientific activities of the American Medical Association with political action, she said. Those political precepts still hold true, and AAPS provides its members with legal consulting services and legislative lobbying through its professional staff based in Burke, Virginia.

Dr. Orient, a 1974 graduate of the Columbia University College of Physicians and Surgeons, served her residency at Parkland Hospital in Dallas, Texas, and prior to opening her private practice, served on the faculty of the University of Arizona and worked for the Veterans Administration Hospital in Tucson.

**Dr. Armando Olivares**, a family practitioner in Holbrook, recently received a certificate of appreciation for his volunteer work with Arizona's Special Olympics program. The certificate was signed by Senator Edward M. Kennedy and Eunice Kennedy Shriver, president of the National Special Olympics Foundation.

Dr. Olivares, who has worked with the Special Olympics program for more than 10 years, was nominated for the 1986 Arizona Special Olympics Award in the Outstanding Adult of the Year category. He was nominated based on his years of service as a volunteer physician for the Special Olympics and was cited for his compassion, dedication and distinguished services to the lives of mentally handicapped children.

**Ronald P. Spark, M.D.**, a pathologist at Tucson Medical Center, has been selected as a Charter Member of the National Association of Physician Broadcasters (NAPB). This honor is in recognition of Dr. Spark's work as co-founder and moderator of the Pima County Medical Society's (PCMS) weekly radio program and cable TV series, both entitled "Prescription for Health." Dr. Spark is also a recipient of the Tucson press Club's Orchid Award for Media Excellence.

The NAPB will serve "Media-Docs" as a forum for ethical and technical exchange. Approximately 400 physicians struggle to maintain an active clinical practice as well as work in the electronic media.

Dr. Spark has served the PCMS as as its President and Chairman of its Media Committee. Most recently he has appeared on radio and television as an advocate for the Tucson Fund Raising Review Board, for which he currently serves as Chairman.

**Wm. James Howard**, Director of Medical Education at Good Samaritan Medical Center in Phoenix, has been appointed to the Executive Committee of the Alumni Association of Haverford College in Haverford, Pennsylvania.

Howard, also a clinical professor of medicine at the University of Arizona, has been involved in medical education at Good Samaritan for the past ten years. Before that he served as associate chief of the University of Pennsylvania Medical Service at Philadelphia General Hospital.

A member of the American College of Physicians and the Endocrine Society, Howard also is a past president of the Arizona affiliate of the American Diabetes Association. He serves on the boards of the Arizona Chapter of the American Heart Association and the Central Arizona Chapter of the American Red Cross.

Following his graduation from Haverford in 1960, Howard received his M.D. degree from the University of Pennsylvania School of Medicine.

**Dr. Sanford Roth** of Phoenix, an internationally recognized authority on arthritis, has been named chairman of the Clinical Trials Committee of the Pan American League Against Rheumatism (PANLAR).

Dr. Roth, founding director of the Arthritis Center, Ltd., and a medical director of the Arizona Institutes, received the honor during a November PANLAR meeting in Buenos Aires. His four-year committee appointment includes a liaison assignment to the International League Against Rheumatism, based in Basel, Switzerland.

Considered one of the nation's leading experts on rheumatoid arthritis, Dr. Roth participated in the formation earlier this year of The Arizona Institutes, a Phoenix-based medical association specializing in treatment of arthritis and related bone, joint and muscle injuries and disorders.

A medical graduate of Ohio State University, Dr. Roth is a fellow of the Mayo Clinic Graduate School of Medicine and provides consulting services to the Arthritis Advisory Committee of the U.S. Food and Drug Administration.

Also, Dr. Roth directs the Arthritis Rehabilitation Program at St. Luke's Hospital and functions as medical research director for Harrington Arthritis Research Center. His primary work at the Arthritis Center, which he founded in 1966, serves as a cornerstone of The Arizona Institutes' medical program.

The Arizona Institutes, headquartered at 3330 North Second Street, includes five Valley-wide treatment centers and 15 neighborhood clinics.

Physician groups associated with The Arizona Institutes in addition to The Arthritis Center include The Arizona Institute of Hand and Plastic Surgery, Ltd.; The Institute for Bone and Joint Disorders, P.C.; and The Arizona Institute for Footcare Physicians, P.C.

**Don V. Langston, M.D.**, Glendale, has been reappointed to a three-year term on the National Advisory Council for Women, Infants and Fetal Nutrition (WIC), as well as to the national advisory committee for the Commodities Supply Food Program.

Dr. Langston was first appointed to the National WIC Council in 1983 by U.S. Secretary of Agriculture, John R. Block. The Advisory Committee meets several times a year, either in person, by telephone conference or through correspondence, to make recommendations about the

nutrition program to the federal Agriculture Secretary.

The WIC program is designed to provide nutrition to pregnant women, nursing mothers, infants and children up until age five in an effort to improve health and eliminate medical problems which drain public health care resources. The program operates with a $1.58 billion annual budget which is exempt from the cutbacks of the Gramm-Rudman legislation. In order to qualify for nutritional benefits provided through the program, participants must be both nutritionally and economically in need.

In addition to their ongoing advisory function, the committee members produce a bi-annual report to the President and the Congress on the status of the WIC program and make recommendations for changes.

The membership of the committee is specified in its enabling legislation. Dr. Langston is the committee's designated pediatrician. Membership also includes an obstetrician, three program participants and representatives from an Indian tribal organization, a non-profit organization, a migrant clinic, the U.S. Department of Health and Human Services, the U.S. Department of Agriculture, a state health department director and state WIC director.

## Jane Goodall at ASU

Anthropologist **Jane Goodall, Ph.D.**, will talk about her research with African apes at 7:30 p.m., Wednesday, April 29, in Grady-Gammage Auditorium on the Arizona State University campus, Tempe.

Dr. Goodall's presentation, "In the Shadow of Man," based on her work in Nairobi and Gombe, is sponsored by the College of Liberal Arts and the Department of Anthropology. Her program is open to the public.

Tickets are $9.00 and $11.00 at Gammage Box Office and Dillards.


# The 96th Annual Meeting

of the

# Arizona Medical Association

will be held

June 4 - 6, 1987

at

The Pointe at South Mountain

7777 South Pointe Parkway, Phoenix, Arizona

THURSDAY, JUNE 4
All Day
Current Perspectives
C.M.E. Programs

Evening
Casual Reception
Dinner

FRIDAY, JUNE 5
6 a.m., Executive Committee
8 a.m., Board of Directors
10 a.m., House of Delegates

Noon, Past Presidents' Luncheon
2 p.m., Reference Committees
President's Reception & Banquet

SATURDAY, JUNE 6
8 a.m., House of Delegates
Noon, Board of Directors

## Dear Editor:

I recently had the opportunity to address the Board of Directors of ArMA and hope such appearance resulted in a greater understanding by physicians of the role of the PRO and H.S.A.G.

It is my impression that the questions presented me indicate concern in the following areas:

1. Is review being done in a manner which assures fairness and competence?
2. Is there adequate provision for the appeal of decisions?
3. Is there some ulterior motive, pecuniary or otherwise, which influences medical review by H.S.A.G.?
4. Is the PRO program so off base in relation to provision of good medical care that it is best ignored by practicing physicians?

You are well aware of my belief that medical review by the government is a reality and that there is no question whether it shall or shall not be done, but only one as to who will do the review. In that setting, I think H.S.A.G. is presently and could be even more so in the future a reasonable choice to interface between government regulations and quality medical care. If such is not the case, then it would seem to me it behooves everyone to make it so. If, in the future, the Arizona Medical Association is convinced that H.S.A.G. is simply not capable or willing to provide the kind of medical review that is acceptable to physicians then certainly it should make these feelings known and do everything possible to replace H.S.A.G. with a group which would be more acceptable. This, I feel certain, should be another organization of local physicians rather than the Fiscal Intermediary or an out of state physicians' group.

To make certain that the present system works correctly, we encourage, as much as possible, participation of members of ArMA. Certainly some of the concerns voiced which would suggest that due process is not followed could be assuaged by participation of more practicing physicians unassociated with H.S.A.G. in making review decisions. In the final analysis, however, it is the responsibility of the Board of Directors of H.S.A.G. to review decisions made by reviewing physicians if those reviewing physicians have found what they consider to be aberrant behavior.

Some of the comments which suggested that it was only fair for physicians who are "criticized" to be able to sit across the table from their "accusers" are simply not manageable. When physicians, either by their request or ours, appear before H.S.A.G. committees it is the role of the committee to consider whether decisions made at a lower level are appropriate. It is at this level that additional input, perhaps and hopefully through ArMA, would be of great value. Assuming that physicians who have no vested interest in the success or failure of H.S.A.G. were to take part in these hearings, I would think the best interest of the medical community would be served. Perhaps you could also consider this possibility.

I had no time during my presentation to inform the audience of additional actions which will be required of the PRO in the coming months. As you probably know, there will be mandatory Second Opinion Programs for some ten surgical procedures. There will also be mandatory precertification of the need for assistant surgeons during the performance of cataract surgery. There may be involvement of H.S.A.G. in the review of care provided by prepaid health plans to Medicare beneficiaries which would include outpatient review. Laws and regulations are not made by H.S.A.G. The presence of H.S.A.G. on the local scene hopefully allows practicing physicians the ability to see that the implementation of regulations is done in as reasonable a fashion as possible. I would beseech the Arizona Medical Association to become an active participant in the PRO program for the benefit of its membership and their patients.

Lawrence J. Shapiro, M.D.
President, H.S.A.G.

## Adequacy of Psychiatric Treatment in Non-specialty Setting

Non-psychiatric physicians prescribing anti-depressants for medical-surgical inpatients use the drugs "infrequently and with little rigor," treating depression similar to pain, reports a study in February's *Archives of General Psychiatry*. Regardless of the reason for use, non-psychiatrists were found to use relatively low dosages of anti-depressants, rarely plan or make dosage increases, and rarely discontinue medication, Allan L. Callies and Michael K. Popkin, M.D., of the University of Minnesota Medical School, Minneapolis, find. In a related study, Jacqueline Wallen, PhD, of the National Center for Health Services Research and Health Care Technology Assessment, Rockville, Maryland, and colleagues, examined the rate of psychiatric consultations in a national sample of short-term general hospitals. They found it to be low compared with the frequency of diagnosed secondary psychiatric conditions, as well as in comparison to published reports of the inpatient prevalence of mental disorder and consultation rates reported elsewhere.

## Diabetes and Stroke Risk

Diabetes seems to be an independent risk factor for thrombolytic (blood clot-caused) stroke, and diabetes that is poorly controlled or of long duration adds to the risk, a study in a recent *Journal of the American Medical Association* reports. Robert D. Abbott, PhD, of the National Heart, Lung and Blood Institute, Bethesda, Maryland, and colleagues, base the conclusion on data from the Honolulu Heart Program, a long-term cardiovascular disease study. The report involved 690 diabetic men and 6,900 non-diabetic men free of coronary heart disease and a history of stroke. After 12 years of follow-up, the relative risk of clot-related stroke in the diabetics was twice that of the non-diabetics. Control of hypertension, heart attack and other risk factors did not reduce the risk, the report says. "Our results," it concludes, "indicate the need for medical approaches beyond routine managemt of risk factors in the patient with diabetes in an attempt to change a broader risk-factor profile that may affect unknown causal links between diabetes and stroke."

## Cocaine's Effect on the Fetus, Heart

An animal study in a recent *Journal of the American Medical Association* says maternal use of cocaine during pregnancy reduces uterine blood flow and impairs oxygen flow to the fetus, causing fetal hypertension and other cardiovascular changes. The study, by James R. Woods, Jr., M.D., now of the University of Rochester School of Medicine, and colleagues at the University of Cincinnati, involved pregnant ewes. Administering cocaine produced dose-dependent increases in maternal blood pressure and decreased uterine blood flow. Direct cocaine administration to the fetus produced smaller increases in fetal heart rate and blood pressure, the report says. In JAMA's Questions and Answers section, David C. Hueter, M.D., of Northwestern University Medical School, Chicago, also addresses cocaine's cardiovascular effects. A growing body of evidence relates cocaine to clinical ischemic heart disease, probably through a number of mechanisms, he notes. While little is known about the long-term prognosis of such problems, "clearly, avoiding further cocaine abuse should be the keystone to long-term treatment," Hueter says.

## New Computer Graphics System to Study Cornea

A report in February's *Archives of Ophthalmology* describes a new computer analysis system designed to improve eye surgery and research by producing color-coded maps of corneal surface power, or how well the cornea acts as a lens. These contour maps make it easier to spot subtle distortions and should allow improved analysis and refinement of corneal surgery techniques, report Leo J. Maguire, M.D., now of the Mayo Clinic, Rochester, Minnesota, and colleagues at the Louisiana State University Medical Center School of Medicine, New Orleans. The system produces

high-resolution detailed topographic maps from keratoscope pictures of the corneal surface. "Improved corneal topography analysis," the study says, "should find wide clinical application in the study of refractive corneal surgery techniques and in the study of corneal disorders that cause irregular astigmatism.

## Presculpted, Banked Cartilage for Middle Ear Reconstruction

Using banked, presculpted rib cartilage from cadaver donors is an effective means of rebuilding the bones of the middle ear for hearing restoration, says a study in the February *Archives of Otolaryngology-Head and Neck Surgery*. The preshaped homologous transplants, further fitted in the operating room to meet a patient's anatomic needs, are as effective as plastic materials for reconstruction but are not resorbed or extruded over time, as occurs with the artificial implants, says Richard A. Chole, M.D., Ph.D. of the University of California-Davis. Chole studied 102 reconstruction procedures using the banked cartilage. Of the 51 transplants available for follow-up after three years, nearly 97 percent of the initial hearing improvement was maintained. In addition, no transplants were extruded or "rejected" as a result of a foreign-body reaction, Chole says, and resorption was minimal.

## Physicians Could Help Reduce Gun Threat to Children

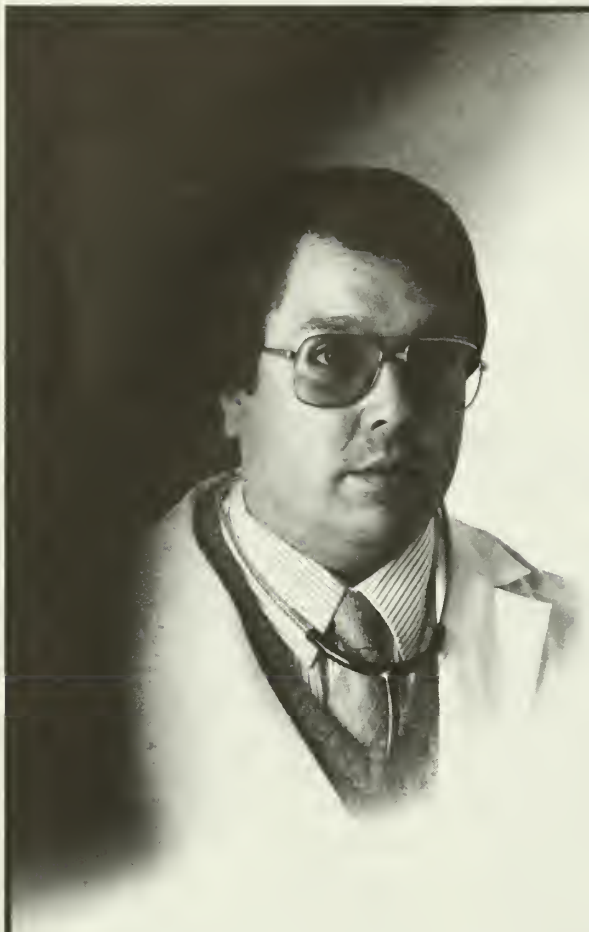
Physicians should play a key role in efforts to reduce the safety threat that guns in the home pose to children, says a report in February's *American Journal of Diseases of Children* [*AJDC*]. Patti J. Patterson, M.D., and Leigh R. Smith, M.D. of the University of Texas Medical Branch (UTMB), Galveston, say doctors—especially pediatricians—have successfully promoted child safety laws for automobiles, poisons and flammable fabrics; "a similar effort should be made with regard to firearms." Patterson and Smith surveyed 150 families from the UTMB pediatric outpatient clinic and found that 38 percent kept at least one gun in the home; more than half this group said the gun was loaded at all times and 10 percent said it was loaded, unlocked and within a child's reach. Despite a limited study sample, "the overall importance of household firearms as a threat to safety should not be overlooked," the authors say.


**Announcement of the**
**XXXIV ANNUAL SYMPOSIUM**
**of the**
**MEDICAL SOCIETY OF THE UNITED STATES AND MEXICO**
**April 29-30, May 1-2, 1987**
**Hotel San Felipe Mision**
**Oaxaca, Mexico**

**Scientific Topics Include:**
- Evaluation of the Polio Treatment Program in Malawi, Central Africa
- Cocaine from the Slopes of the Andes to Oaxaca
- Magnetic Resonance Imaging
- AIDS
- Advantages and Disadvantages of Cartoid Artery Surgery
- Use of the Lithotripter in Renal Stones and Gall Bladder Stones
- Use of Aortic Allografts
- Plus other interesting and provocative subjects

**Social Program Will Include:**
- Welcome Cocktail Party & Dinner
- Inaugural Dinner & Ball
- All-Day Guided Tour to Ruins
- Day Tour for Spouses Including Sightseeing and Shopping

**For more information and registration forms, contact: Mrs. Beverly Richter, Medical Society of the United States and Mexico, 810 West Bethany Home Road, Phoenix, AZ 85013, (602) 246-8901**



## Extended Care: No. 4 in a Series

# "Hospital costs can be as debilitating as any illness or injury. That's why the trend is to provide rehab services in an extended care center."

**– John C. Porter, M.D.**
**Medical Director**
**Lincoln Health**
**Rehabilitation Services**

"Given the high costs and high pressures to discharge patients from acute care, many physicians are faced with a dilemma: how to provide for the rehabilitative needs of the subacute patient who isn't ready for home care.

"Extended care centers exist for this very reason. At Bryans Center or Helen C. Lincoln Care Center, for example, extensive hospital-like rehab programs with a coordinated team approach includes physical therapy, speech-language pathology, occupational therapy, and other support services. And without hospital overhead, extended care room rates are significantly lower.

"Physicians enjoy the benefits of having patients centralized under one roof, closely monitored, with next-door access to acute care services. The success of our coordinated team approach is confirmed by the fact that our extended care patients return home to lead healthy, productive lives.

"If you're concerned with cost vs. quality of life issues, I urge you to explore the extended care alternative today."

## Get the Facts about Extended Care!

Call or write for your free copies of the Bryans Center or Helen C. Lincoln Care Center portfolios and the latest Medicare guidelines for nursing homes. Ask one of our administrators or social service directors for assistance with your patients – they can help with everything from extended and long-term care to a full range of rehabilitation services, even home health or adult day care. Call us or stop by for a personal tour...you'll like what you see!

**Adjacent to John C. Lincoln Hospital**

Located just steps away from John C. Lincoln Hospital & Health Center, Bryans Center has full access to the resources and specialty services of the hospital. It features one of the largest therapy areas of any skilled nursing facility in Arizona.

**Administrator: Lynn Davies**

**944-1666**

BRYANS CENTER

9155 North 3rd Street
Phoenix, AZ 85020-2460

**Adjacent to Thunderbird Samaritan Hospital**

Located on the Glendale campus of Thunderbird Samaritan Hospital & Health Center, adjacent to retirement communities, medical offices and shopping. Authentic antiques add charm to the quiet comfort of this self-contained community.

**Administrator: Sid Roberts**

**843-8433**

HELEN C. LINCOLN EXTENDED CARE CENTER

13620 North 55th Avenue
Glendale, AZ 85304-1399

Affiliates of Lincoln Health Resources

# New Active Members . . .

*The Arizona Medical Association welcomes the following new members:*

**COCHISE**

**Tae-Uk Cho, M.D.**
Anesthesiology
P.O. Box 2798, Sierra Vista
Korea University Medical
College - 1973

**COCONINO**

**Garry R. Greene, M.D.**
Anesthesiology
1215 North Beaver Street
Flagstaff
University of Washington
School of Medicine - 1978

**GILA**

**William K. Peck, M.D.**
Radiology
807 South Ponderosa
Payson
New York University
School of Medicine - 1943

**MARICOPA**

**Terry Clayton, M.D.**
Anesthesiology
3030 South Rural Road
Tempe
University of Utah
College of Medicine - 1983

**Edward H. Kowaleski, M.D.**
Family Practice, Sports Medicine
13200 North 103rd Avenue
Suite 7, Sun City
Wayne State University
School of Medicine - 1979

**Marie Mesaros, M.D.**
Anesthesiology
1040 East McDowell, Phoenix
Medical College of
Pennsylvania - 1965

**Robert L. Moss, M.D.**
Anesthesiology
1845 South Dobson
Suite 213, Mesa
Medical College of
Wisconsin - 1980

**Jeffrey M. Pont, M.D.**
Internal Medicine
6135 North 7th Street, Phoenix
Wayne State University
School of Medicine - 1982

**John C. Porter, M.D.**
Physical Medicine &
Rehabilitation
2021 North Central
Suite 103, Phoenix
Fac De Med/La Univ de
Nuevo Leon - 1981

**Robert J. Spies, M.D.**
Plastic Surgery, General Surgery
10565 North Tatum Boulevard
Suite B-116, Paradise Valley
Ohio State University
College of Medicine - 1979

**Jeffrey M. Taffet, M.D.**
Otorhinolaryngology
3411 North 32nd Street
Phoenix
Univ De Monterrey Inst
Cien De La Sal - 1979

**PIMA**

**Gregory J. Boulanger, M.D.**
Anesthesiology
5200 East Grant Road
Suite 602, Tucson
Medical College of
Wisconsin - 1981

**William P. Diefenbach, M.D.**
Neurological Surgery
5402 East Grant Road
Tucson
Columbia University
College of Physicians
and Surgeons - 1979

**John W. Hesser, M.D.**
Obstetrics & Gynecology,
Maternal/Fetal Medicine
5200 East Grant Road
Bldg. No. 800, Tucson
University of Colorado
School of Medicine - 1972

**Joseph Latack, M.D.**
Radiology
3170 East Fort Lowell
Tucson
University of Michigan
Medical School - 1969

**Eve C. Shapiro, M.D.**
Pediatrics, Adolescent Medicine
529 West Wetmore Road
Tucson
State University of New York
College of Medicine,
Syracruse - 1976

**David R. Siegel, M.D.**
Neurology
1601 North Tucson Boulevard
Suite 2, Tucson
University of California
Los Angeles School of
Medicine - 1979

**Thomas J. Tilsner, M.D.**
Otorhinolaryngology
6546 Carondelet, Tucson
University of Minnesota
Medical School - 1971

**Paul R. Vanatta, M.D.**
Pathology, Clinical Pathology
6200 North La Cholla
Boulevard, Tucson
University of Texas
Southwestern Medical
School - 1978

**Merri B. Morris, M.D.**
Obstetrics & Gynecology
1820 East Florence
Boulevard, Casa Grande
University of Arizona
College of Medicine - 1982

**YUMA**

**Herman M. Fountain, M.D.**
Emergency Medicine
2400 Avenue A, Yuma
University of Miami
School of Medicine - 1973

**NEW ASSOCIATE MEMBERS**

**MARICOPA**

**Scott C. Benson, M.D.**
Family Practice
P.O. Box 1387, Mesa
University of Arkansas
College of Medicine - 1948

**Alvin M. Kurzon, M.D.**
Obstetrics & Gynecology
4303 East Cactus Road
Phoenix
Medical College of
Wisconsin - 1943

**NEW RESIDENT MEMBERS**

**MARICOPA**

**Paul R. Barnard, M.D.**
Pulmonary Diseases,
Internal Medicine
Good Samaritan Medical Center
Creighton University
School of Medicine - 1982

**Janice Dorn, M.D.**
Psychiatry
Maricopa County Medical Center
Univ Autonoma De
Ciudad Juarez - 1982

**Samuel W. Downing, M.D.**
Family Practice
Phoenix Baptist Hospital
University of Colorado
School of Medicine - 1985

**Daniel Gee, M.D.**
Anesthesiology
7748 East Granada
Scottsdale
University of Arizona
College of Medicine - 1983

**Thomas W. Grahm, M.D.**
Neurological Surgery
St. Joseph's Hospital and Medical Center
University of Texas School of Medicine, Galveston - 1983

**Kathleen W. Jones, M.D.**
Internal Medicine
Good Samaritan Medical Center
Indiana University School of Medicine - 1984

**Delwyn J. Worthington**
Orthopedic Surgery
Maricopa County Medical Center
University of Arizona College of Medicine - 1982

**PIMA**

**Sandra M. Clark, M.D.**
Family Practice
1450 North Cherry Street
Tucson
Temple University - 1978

**Scott Krasner, M.D.**
Occupational Medicine, Obstetrics & Gynecology
1445 North Warren Avenue
Tucson
Medical College of Wisconsin - 1983

## NEW STUDENT MEMBERS

### PIMA — UNIVERSITY OF ARIZONA COLLEGE OF MEDICINE

**Michael F. Allen**
3700 North 1st Avenue
Suite 1121, Tucson

**Irene B. Flahie**

**Patrick S. Freeman**
1487 East Hampton
Suite B, Tucson

**Jennifer A. Harvey**
2601 West Broadway
Suite 598, Tucson

**Amy J. Kenrick**
720 North Longfellow Avenue, Tucson

**David King**
142 South Tucson Boulevard
Suite 9A, Tucson

**David A. Pedersen**
449 East Smoot Drive
Tucson

**Stephen A. Shapiro**
1201 East Drachman Street
Tucson

**Marie South**
2146 East Hawthorne Road
Tucson

**Karen Vournas**
5701 East Gleen
Suite 74, Tucson

**Keith Wharton, Jr.**
3015-1 North Olsen
Tucson


# MEDICAL BOOKSTORE

**MEDICAL BOOKSTORE**
College of Medicine
Arizona Health Sciences Center
Tucson, Arizona 85724
Phone: 626-6669

## *PRACTICE MANAGEMENT PROBLEMS?*

### DO ANY OF THESE SOUND FAMILIAR?

- Declining Patient Volume and Practice Income
- Increasing Overhead
- More Competition Than Ever Before
- Demanding Patients
- Confusion Over Governmental Reimbursement Plans
- Skyrocketing Malpractice Insurance Premiums
- Confusing Contracts from Prepaid Health Plans

While it may not be possible to eliminate all of these problems, it is possible for medical practices to control at least a portion of these challenges through effective Practice Management.

The Professional Practice Division of Toback & Company can provide marketing advice which will increase patient volume; financial tools to increase income and control overhead; reduce office conflict and personnel management problems, reducing employee turnover; and increase physician satisfaction with the practice. Richard E. Kirkpatrick, M.H.S.A., Manager of our Professional Practice Division and a nationally recognized authority on medical practice management can provide you with additional information on the benefits of our services in a no-fee interview. Please call 264-9011 to schedule an appointment.

**TOBACK & COMPANY, P.C.**
Professional Practice Division
3200 North Central Avenue, Suite 700
Phoenix, Arizona 85012
(602) 264-9011

Richard E. Kirkpatrick

# The Teaching of Geriatric Medicine in the Nursing Home

The Dean's Page has recently reported on the changing forces affecting the education of physicians. Shorter stays for sicker patients in teaching hospitals together with much more sophisticated outpatient medical care is forcing colleges of medicine to move their major teaching emphasis to the outpatient clinic. Below we consider yet another force affecting the locale for the education of students and residents of medicine: the care of the elderly.

The demography of aging has become familiar to most of us. In the United States the over 65 segment of our population has grown from 3 million persons in 1900 to 25 million in 1980. By the year 2030 almost one quarter of Americans will be over age 65. The 85-plus population is increasing even more rapidly with a seven-fold increase projected by the middle of next century. This growing number of elderly brings the concomitant problems of increased morbidity and a changing style of care for severe problems of frailty, dementia, incontinence, fractures and multiple illnesses. Nursing homes frequently provide the location for medical response to the long term care needs necessitated by these problems.

Between 1963 and the present, nursing home occupancy by the nation's elderly at any given time increased from 2.5% to 5.0%. One in 20 persons age 65 and over resides in one of the estimated 19,000 nursing homes across the country at an annual bill of over $30 billion. One in 4 persons will use nursing home services at some time during their later years. By the year 2030 the number of residents in nursing homes in the United States will have grown from 1 million to nearly 4 million and the cost will have skyrocketed to over 1 trillion dollars. The remarkable increase in the number of new nursing homes is an obvious confirmation of the trends. However, these trends have had little impact on medical education. Knight Steel, M.D., former president of the American Geriatrics Society, pointed out that until a few years ago the number of medical faculty providing either service or teaching within a nursing home approached zero.

The development of teaching nursing homes associated with medical schools is both an opportunity and a necessity. As teaching hospitals concentrate on acutely ill and exceedingly complex patients for ever shorter periods of time, the opportunities for teaching basic medicine, especially to beginning medical students, becomes limited. Shift of student training to outpatient clinics will be the primary response of medical schools, but outpatient care does not lend itself to the thorough examination and meticulous review which is so necessary for teaching the fundamentals of medicine. The teaching nursing home provides an opportunity to introduce students to a less hurried approach to comprehensive care.

Physicians will find a greatly increasing portion of their time devoted to nursing home care, yet at present our graduates have received almost no training to prepare them for the unique problems and opportunities to be found there. Classically, nursing homes have been the instrument of nurses. Physicians have traditionally limited their involvement in the nursing home. In the future the physician will take on a larger role, more akin to present physician activities within the acute hospital. The most striking difference will be that care provision will be much more collaborative in nature using teams consisting of nurses, social workers, physical therapists and other aides who are so essential to quality care of the nursing home resident.

Teaching nursing homes like the teaching hospital as it exists today will make up only a small proportion of the nation's institutions. Critics have appropriately worried that costs in a teaching nursing home will be higher than comparable nursing homes. While this is undoubtedly true, it is no more true for the teaching nursing home than for the teaching hospital and is a justifiable price for the education of physicians who must perform with ever higher standards.

Also like the teaching hospital, the teaching nursing home will be concerned with research. Research among nursing home residents, as with their medical care, must be selected with the individual's quality of life and personal wishes ever in mind.

The problems of dementia, incontinence, poor mobility, rehabilitation of the elderly, the ramifications of polypharmacy, depression and improvements in socialization are but a few of the areas that have begun to be studied and which are appropriate for the improvement of the quality of life of nursing home residents.

These issues are now being approached by medical schools throughout the United States and the University of Arizona. The evolution of the medical curriculum has already demanded an increased emphasis on geriatrics. The addition of a Teaching Nursing Home will be a major step toward our goal of improving care of the elderly. ■

John T. Boyer, M.D.
Director
Restorative Medicine
Theodore H. Koff, Ed.D.
Director
Long Term Care Gerontology Center
Louis J. Kettel, M.D.
Dean
College of Medicine
University of Arizona


# ARIZONA PHYSICIANS' DIRECTORY

**ALICE E. PALMER, M.D.**
**Diplomate of the American Board of Dermatology**

**Announces the Association of**
**TAMELA B. TRIPP, M.D.**
**in the practice of**
**Dermatology and Dermatologic Surgery**
**at the**

**Plaza Del Rio Complex**
**13460 N. 94th Drive, Suite K-5**
**Peoria, Arizona**
**(602) 972-5853**

**SPECIALIZING IN QUALITY ASSURANCE.**

Physician Office Laboratory Testing leads to increased Medical Practice Efficiency by providing better patient care, increased patient convenience, increased physician convenience and rapid test results for faster diagnosis.

Let Associated Laboratory Consultants assist you in:
- Maximizing Your Existing Laboratory
- Proper CPT Code Usage
- Developing A New Laboratory
- Generating New Income

SERVICES
LABORATORY
Development • Implementation • Management
PERSONNEL
Recruitment • Evaluation • Education

ASSOCIATED LABORATORY CONSULTANTS
(602) 990-0068
P.O. Box 502, Scottsdale, Arizona 85252

# Classified Advertising


**We Bind Your**
**PERIODICALS**

Preserve your medical journals as beautifully bound books. Choose from 30 different colors of durable Library Buckram.

**$14.50 per volume, (name imprint $1.00)**
**$15.50 Imitation Leather, (rules .50 each)**

Inquire about quantity discounts. **Free** local pickup and delivery on 10 volumes or more. Minimum order is $25.00.

**ROSWELL BOOKBINDING**
**2614 North 29th Avenue**
**Phoenix, Arizona 85009 ■ (602) 272-9338**

P A S

*"People, The Reason And The Key"*

**Personnel Administration Services, Inc.**
3080 North Civic Center, Suites 11 & 12
Scottsdale, Arizona 85251

(602) 947-8053
(602) 947-8375

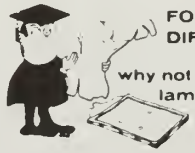
**EDWARD N. PHILLIPS**
President

**DANNY T. SEIVERT**
**INSURANCE, INC.**
Professional Programs
for Professional People
**70 E. Mitchell Dr., Suite 6**
**Phoenix, Arizona 85012**
**263-9090**

**MEDICAL SPACE AVAILABLE**
**at the**
**PROFESSIONAL CENTER**
2610 West Bethany Home Road (At I-17)

Managed by
Public Management & Appraisal
(602) 249-9072

YOU WORKED HARD



FOR THAT DIPLOMA..
why not have it laminated?

it will last a lifetime....
**THE PLAQUE SHOP**

Wood ploques — Reody to hang
No glass to breok — Moisture proof
Dirt proof -- Impressive.
Our ploques ore monufoctured locolly

**ARIZONA LAMINATING SERVICE, INC.**
**7231 East First Avenue**
**Scottsdale, Arizona 85251**
**(602) 945-9338**

## PROFESSIONAL OPPORTUNITIES

### ARIZONA FAMILY PRACTICE—BC/BE

For rapidly expanding practice. Early shareholder. Bilingual is important. Submit CV to: 809 E. Washington #105, Phoenix, Arizona 85034.

### EXPAND YOUR PRACTICE SUN CITY OFFICE TO SHARE

A fully equipped & staffed office, 4 exam rooms, in a large medical building adjacent to Boswell Memorial Hospital is available full or part time. Ideal for an established physician who would like an additional office. Call (602) 977-0518.

### MEDICAL PRACTICE SALES AND APPRAISALS

We specialize in the valuation and selling of medical practices. If interested in buying or selling a medical practice, contact our Brokerage Division at The Health Care Group, 400 GSB Building, Bala Cynwyd, PA 19004; (215) 667-8630.

### FAMILY PRACTICE

To do family care in multi-specialty clinic and satellite clinic. Full in-house lab and x-ray. Delightful community, good schools and recreation. Reply to: P.O. Box 0955, C/O Arizona Medicine, 810 West Bethany Home Road, Phoenix, Arizona 85013.

## MEDICAL OFFICES

### FOR SALE

Established Tucson Radiology office on Health Care Campus. Retiring Radiologist will introduce. High gross receipts. No nights or weekends. T.V. Suite (2) and U/S. Reply to ArMA, P.O. Box 3117, Phoenix, Arizona 85013.

### BUILD YOUR OWN

65th Avenue & Camelback, Phoenix, Arizona. Prime C-O lot at 6535 West Camelback Road. 105x170 gross. Share existing 133 parking spaces with adjacent Dental/Medical Building. Only $134,000. Call Jeanie Phipps, (602) 942-2010 or **JOHN HALL & ASSOCIATES**, (602) 242-6377.

### PROFESSIONAL SUITES AVAILABLE

Approximately 1100 square feet. Across rom Valley West Mall. Glendale Professional Building. (602) 939-8311.

### MEDICAL OFFICE

Modern, nicely furnished medical office to share. Available two/three days per week. Located in rapidly growing area of Mesa. For information call (602) 345-7543.

## REAL ESTATE

### HOME FOR SALE

Altogether gracious, spacious and charming custom home in the pecan groves of Tempe. Features include four bedrooms, 3¾ baths, plus: *Exterior:* Custom rock fireplace chimneys, stucco planter boxes, lanai, bay windows, underground air returns, 2x6 exterior walls, wood casement & bronzed duopane windows, self-cleaning pool, automatic sprinkler system. *Interior:* Oak cabinets & doors, wet bar, vaulted, beamed, tongue & groove ceiling in family room, overhead planter shelves in galley w/indirect lighting, gold-plated fixtures in baths, skylights throughout, zoned air conditioning, walk-in closets, built-in sub-zero refrigerator w/oak exterior, built-in microwave and compactor, kitchen island, parquet floors in kitchen & galley, security system, coffered ceiling in dining room, etc., etc! $487,500. Realty Advisers (602) 838-1800; Barbara Grant (602) 839-7786.

## MISCELLANEOUS

### FOR SALE

Due to remodeling and lack of space, doctor has many items for sale. Included are a Baush & Laumb Polarizing Microscope, Centrifuge, Nepholometer and other lab supplies. Also included are a desk, chairs, end tables and other office furniture. To inquire please call (602) 246-1964 and ask for Rosemary.

### FAST GROWING NATION-WIDE FRANCHISE

Sale and Delivery of Teddy Bears — All occasions. For Sale: Mesa Store & Franchise. Perfect for family, 2nd income or woman's start-up business. Call owner (eves.) (712) 225-2131. Est. investment — $50,000. (See Display Ad)

### LAB EQUIPMENT FOR SALE

Blood chemistry analyzer: Gemstar unit by Electronucleonics — efficient blood chemistry panels and/or individual chemistries. Used less than 18 months. $8,000 or best offer. Please call (602) 963-2340 between 8:00 a.m.—6:00 p.m. Tempe/Chandler location.

### LARGE LOANS

Since 1966 specializing in large loans to physicians nationwide from $15,000.00 to $90,000.00. Long repayment terms at fixed interest rates. Commitments usually within 48 hours. Woodside Capital Corp., Woodside Capital Building, P.O. Box 368, Woodland Hills, CA 91365. For further information call (800) 423-5025.

### PHYSICIANS SIGNATURE LOANS

Loans to $50,000. Competitive fixed rates. No collateral. Up to seven years to repay with no pre-payment penalties. Prompt, courteous service. Physicians Service Association, Atlanta, Georgia (800) 241-6905. Serving MDs for over ten years.

*Classified ad rates are $20 for the first 50 words or less and 20 cents for each additional word. Send to: ArMA, 810 West Bethany Home Road, Phoenix, Arizona 85013.*

Clinical Investigation

# Blue-Yellow Vision Deficits in Patients With Diabetes

MELISSA ROCKETT, MSN; DOROTHY ANDERLE, MSN, *and* ALICE N. BESSMAN, MD, *Downey, California*

*Home blood glucose monitoring has been introduced as a means to achieve good control in patients with diabetes mellitus. Many patients use color-reagent strips and color comparisons to determine blood glucose levels. Intact color vision in the blue-yellow range is necessary for accurately interpreting these strips.*

*Blue-yellow vision deficits occur as a consequence of eye disease and are not genetic or sex-linked. We evaluated blue-yellow vision acuity in 70 diabetic patients and in 19 age-matched control subjects. The patients with diabetes were subdivided according to their degree of retinopathy as follows: no disease (N = 14), nonproliferative diabetic retinopathy (N = 16), proliferative diabetic retinopathy (N = 14) and postlaser-treated (N = 26). None of the control group had deficits. Each group of diabetic patients had a statistically significant increase in color vision deficits compared with the controls. In the laser-treated group, deficits occurred in most patients, were more severe and were significantly increased over all other diabetic subgroups. These deficits may impair visual interpretation of home blood glucose monitoring strips.*

(Rockett M, Anderle D, Bessman A: Blue-yellow vision deficits in patients with diabetes. West J Med 1987 Apr; 146:431-433)

Recent studies suggest that good metabolic control may prevent or arrest the chronic complications of diabetes mellitus.[1,2] Home glucose monitoring is one means of achieving good metabolic control.[3] Home glucose monitoring can be done with a photoreflectance meter or by visual interpretation using chemical reagent strips. These reagent strips react with serum glucose to develop two colors simultaneously. Using the visual interpretation method, the colors on the strip are matched by eye with a color comparison scale. Accurate interpretation of these strips requires intact color vision. It has been reported in the literature that diabetic patients have an increased incidence of the acquired, non-sex-linked, blue-yellow color vision deficit.[4-10] The purpose of this study was to assess the incidence of acquired color vision deficits in patients with diabetes and to correlate these deficits, if any, with varying degrees of retinopathy.

## Patients and Methods

A total of 70 patients with diabetes mellitus was selected from the inpatient and outpatient services of Rancho Los Amigos Medical Center. Patients giving a history of familial color vision deficits were excluded from the study, as were those with a gross visual impairment. All patients meeting the criteria were included in the study until an adequate number had been entered.

Before testing, each patient had a vision and funduscopic examination to classify the degree of retinopathy and the vision acuity. In cases of macular edema or a vision acuity of less than 20/100 in either eye, that eye was excluded from further testing. On this basis, 135 eyes of the 70 patients were further evaluated. On the basis of funduscopic examination, the patients were divided into four groups: no ocular disease (14 patients), nonproliferative diabetic retinopathy (16 patients), proliferative diabetic retinopathy (14 patients) and status post laser therapy (26 patients). All patients had a funduscopic examination by a physician after dilation of the eyes, and 75% of the examinations were confirmed by an ophthalmologist.

A total of 19 age-matched controls was tested. The average age of the patients with diabetes was $63.4 \pm 10$ years and of the controls $61.5 \pm 11$ years (difference not statistically significant). The average ages of the various subgroups of diabetic patients were also not significantly different from those of the controls.

The American Optical Hardy, Rand and Rittler pseudoisochromatic plates were used to assess blue-yellow vision.[11] Results were recorded according to the developers' instructions. All testing was done under northern sunlight illumination.

## Results

The results of the blue-yellow vision tests of the 70 diabetic patients and 19 control subjects are given in Table 1. None of the control subjects showed evidence of a color vision deficit. Of the 14 patients who had no demonstrable retinopathy, 2 showed mild and 1 moderate deficits. Of the 16 patients with nonproliferative retinopathy, 3 showed mild loss, and of the 14 patients with proliferative retinopathy, 5 had mild and 1 moderate loss. Of the laser-treated patients, most showed some degree of color perception impairment. Of 26 patients, 14 had mild deficits and 8 had strong deficits.

Each group of diabetic patients had a statistically significant increase in blue-yellow vision deficits compared with the control group, and the group that had received laser treatment

From the Division of Diabetes, Department of Health Sciences, Rancho Los Amigos Medical Center, Downey, California, and the Department of Medicine, University of Southern California School of Medicine, Los Angeles (Dr Bessman). Ms Rockett is currently at the University Hospital, New York University School of Medicine, New York, and Ms Anderle is at Rancho Encino Hospital, Encino, California.

Reprint requests to Alice N. Bessman, MD, Rancho Los Amigos Medical Center, Room 256 HB, 7601 E Imperial Highway, Downey, CA 90242.

had a significantly increased loss compared with all other diabetic groups as well (see Table 1).

## Discussion

Good metabolic control of the diabetic state is thought to delay or minimize the development of the chronic complications associated with diabetes mellitus.[1,2] Self-monitoring of glucose levels is one of the methods advocated to achieve metabolic control in the diabetic population. The two blood glucose reagent strips that are used by diabetic patients and professional staff for blood glucose monitoring utilize either green-yellow hues for interpretation or blue-yellow and red hues.[12] The perception of these color hues is affected in acquired dyschromatopsia (color vision defects). Intact color perception is a prerequisite to obtaining reliable information from the reagent strips if the color-comparison method is used. There is some decreased blue-yellow perception with aging,[13] but because our control subjects were age-matched with the patients with diabetes, the differences between the control patients and the diabetic patients cannot be ascribed to age.

Studies in the literature on acquired color vision deficits in patients with diabetes mellitus report variable results, but most have not categorized the patients into groups that separate out laser-treated patients. Barca and Vaccari tested color vision in 25 diabetic patients under various illuminants, but there was no mention of retinopathy.[4] Birch-Cox evaluated color vision before and after laser treatment in seven patients and found an increase in the loss of blue-green discrimination after laser treatment.[5] Thompson and co-workers assessed the color vision of 185 diabetic patients using the American Optical Hardy, Rand and Rittler plate, among other tests.[6] They did not discuss funduscopic examination results, however, other than to mention that the two patients with color vision deficits had retinopathy. Sinha and Bhatia reported on 68 diabetic patients, dividing their patients into two groups: no retinopathy and retinopathy.[7] The retinopathy group was not subdivided by degree of retinopathy. In the 30 patients without retinopathy, they found only one patient with an acquired color vision deficit. Of the 29 diabetic patients with unclassified retinopathy, 4 had blue-yellow vision deficits. Graham and associates studied 48 patients with diabetes for color vision deficits.[8] The retinopathy of these patients was subdivided into the following categories: no retinopathy, simple background retinopathy, and advanced retinopathy, including laser-treated. Mild to moderate blue-yellow deficits were reported in 24 patients and severe color vision deficits were found in 10 patients. Only one patient with retinopathy had normal color vision. Laser-treated patients, however, were not separated from the patients with proliferative retinopathies. Muntoni and colleagues studied patients with insulin-dependent diabetes mellitus without retinopathy and found a 70% incidence of yellow-blue dyschromatopsia in these patients.[9] Lombrail and co-workers tested 103 insulin-dependent patients for blue-yellow color vision.[10] Dyschromatopsia was present in a third of all diabetic patients and in no controls. They reported no significant differences in diabetic patients with and without retinopathy. Patients having had laser therapy were not identified.

TABLE 1.—*Blue-Yellow Color Vision Deficits in Patients With and Without Diabetes Mellitus**

| Color Vision Deficit | | Patients With Diabetes, N=70 | | | | Controls, N=19 |
|---|---|---|---|---|---|---|
| Degree of Retinopathy | | No Disease, Number | Nonproliferative, Number | Proliferative, Number | Post Laser Therapy, Number | |
| Patients | | 15 | 16 | 14 | 26 | 19 |
| No loss | ♂ | 8 | 8 | 6 | 3 | 7 |
| | ♀ | 3 | 5 | 2 | 1 | 12 |
| Total | | 11 | 13 | 8 | 4 | 19 |
| Mild | ♂ | 2 | 2 | 3 | 8 | 0 |
| | ♀ | 0 | 1 | 2 | 6 | 0 |
| Total | | 2 | 3 | 5 | 14 | 0 |
| Moderate | ♂ | 0 | 0 | 0 | 0 | 0 |
| | ♀ | 1 | 0 | 1 | 0 | 0 |
| Total | | 1 | 0 | 1 | 0 | 0 |
| Strong | ♂ | 0 | 0 | 0 | 2 | 0 |
| | ♀ | 0 | 0 | 0 | 6 | 0 |
| Total | | 0 | 0 | 0 | 8 | 0 |
| Probability,* *P* | | | | | | |
| Control versus | | <.05 | <.05 | <.002 | <.001 | |
| No disease versus | | ... | NS | NS | <.001 | |
| Nonproliferative diabetic retinopathy versus | | ... | ... | NS | <.001 | |
| Proliferative diabetic retinopathy versus | | ... | ... | ... | <.001 | |

NS=not significant

*Using $\chi^2$ comparisons.

Despite the impression that color vision loss may be due both to the retinopathy itself and the photocoagulation used in treatment,[6] only one of the previous studies separated the laser-treated patients from nontreated patients to evaluate color vision deficits.[5] And this author evaluated only for blue-green, not blue-yellow deficits. Russell and co-workers have shown that additional vision-related problems, particularly problems with dim lighting, seem to be accelerated by laser treatment. They also raise the issue of the difficulty in distinguishing between a laser effect and progress of retinopathy.[14]

Increased leakage of fluorescein in the posterior chamber in diabetic patients also has been found before retinopathy occurs.[15] Our studies and those of others showed significant color vision losses in patients with diabetes, even before retinopathy could be detected by standard criteria.

In a recent study, Bresnick and associates evaluated inaccuracies of urinary glucose testing using both Clinitest and Diastix. They found that color vision testing identified patients likely to make a large number of urine testing errors.[16] The ability of diabetic patients with blue-yellow vision deficits to accurately interpret blood glucose reagent strips that are in common use for home blood glucose monitoring has recently been evaluated. Patients with diabetes who have color vision deficits, compared with those who do not, showed significant inaccuracies, reading both too high and too low at most blood glucose levels tested.[17]

In our study, we found that patients with proliferative retinopathy showed about a 32% prevalence of mild and a 0.6% prevalence of moderate blue-yellow deficiency. The laser-treated patients showed a 54% incidence of moderate and a 24% incidence of severe blue-yellow deficits. The laser-treated patients were the only ones who suffered severe deficits. The question of whether the pronounced increase in color vision losses in the laser-treated patients is due to the laser treatment or to a more advanced degree of retinopathy requires further study.

In summary, our results confirmed previous studies that showed that diabetic patients with and without demonstrable retinopathy have an increased incidence of acquired blue-yellow dyschromatopsia. Further, our studies have provided new information that there is a substantial increase in both frequency and severity of blue-yellow vision deficits in diabetic patients who have had laser therapy compared with those patients with both nonproliferative and proliferative retinopathy. Because the color-reagent test strips for home glucose monitoring involve accurately interpreting blues and yellows, patients with diabetes should be evaluated for their ability to accurately read these reagent strips if this method of home glucose monitoring is to be used. As an alternative to the use of color-reagent strips, diabetic patients, especially those who have received laser therapy, can use home blood glucose monitoring machines that do not require accurate color perception for glucose level determination.

#### REFERENCES

1. Davidson MB: Importance of diabetic control and home glucose monitoring. *In* Kaplan SA (Moderator): Diabetes Mellitus. Ann Intern Med 1982; 96:635-649

2. West K, Ahuja MMS, Bennett P, et al: The role of circulating glucose and triglyceride concentrations and their interactions with other 'risk factors' as determinants of arterial disease in nine diabetic population samples from the WHO multinational sample. Diabetes Care 1983; 6:361-368

3. Bleicher SJ: Symposium on home blood glucose monitoring. Diabetes Care 1980; 3:57-126

4. Barca L, Vaccari G: Diabetic retinopathy and color discrimination under various illuminants. Modern Problems Ophthalmol 1978; 19:301-304

5. Birch-Cox J: Defective color vision in diabetic retinopathy before and after laser photocoagulation. Modern Problems Ophthalmol 1978; 19:326-329

6. Thompson DG, Howarth F, Taylor H, et al: Defective colour vision in diabetes: A hazard to management. Br Med J 1979; 3:859-860

7. Sinha A, Bhatia R: Color vision in diabetes mellitus. Indian J Ophthalmol 1979; 27:6-8

8. Graham M, Kesson CM, Kennedy HB, et al: Relevance of colour vision and diabetic retinopathy to self-monitoring of blood glucose. Br Med J 1980; 281:971-973

9. Muntoni S, Serra A, Mascia C, et al: Dyschromatopsia in diabetes mellitus and its relation to metabolic control. Diabetes Care 1982; 5:375-378

10. Lombrail P, Cathelineau G, Gervais P, et al: Abnormal color vision and reliable self-monitoring of blood glucose. Diabetes Care 1984; 7:318-321

11. Newell FW: Ophthalmology, Principles and Concepts, 4th Ed. St Louis, CV Mosby, 1978, p 111

12. Aziz S, Hsiang YH: Comparative study of home blood glucose devices: Visidex, Chemstrip bG, Glucometer, and Accucheck bG. Diabetes Care 1983; 6:529-532

13. Verriest G: Recent Advances in the Study of the Acquired Deficiencies of Colour Vision. Florence, Baccinie Chiappi, 1974

14. Russell PW, Sekuler R, Fetkenhour C: Visual function after pan-retinal photocoagulation: A survey. Diabetes Care 1985; 8:57-63

15. Cunha-Vaz JG, Gray JR, Zeimer RC, et al: Characterization of the early stages of diabetic retinopathy by vitreous fluorophotometry. Diabetes 1985; 34:53-59

16. Bresnick GH, Groo A, Palta M, et al: Urinary glucose testing inaccuracies among diabetic patients. Arch Ophthalmol 1984; 102: 1489-1496

17. Anderle D, Bessman AN: Inaccuracies in the interpretation of blood glucose reagent strips by diabetic patients with acquired dyschromatopsia. Clin Res 1987; 35:129A

# Book Review

*The Western Journal of Medicine does not review all books sent by publishers, although information about new books received is printed elsewhere in the journal as space permits. Prices quoted are those given by the publishers.*

## Clinical Information Systems

Bruce I. Blum. Springer-Verlag, 175 Fifth Ave, New York, NY 10010, 1986. 414 pages, $53.50.

With this book, Blum has succeeded in filling a long-felt need for a treatment of clinical information systems that is both authoritative and complete. By reviewing the subject of clinical information systems broadly, his book answers many of the most frequently asked questions about this subject.

The book divides itself naturally into three parts. A discussion of the history of the modern digital computer and a review of its early applications to the health care system sets the stage. The second part deals with modern hardware and software, with data bases and systems implementations. The final part treats hospital information systems, ambulatory care systems and medical decision making. A brief case study of a particular application system at the author's own institution completes the third part.

Although no book can be everything to all readers, this one comes as close as any that I have seen that attempts to deal with the general subject of medical computing. Blum proceeds through the field systematically and from first principles so that no previous experience with computers or related technology is expected of the reader. Yet the book is dense with facts and explanations, so that at once it is an encyclopedia, a smoothly reading text and a valuable source for the casual reader interested in the uses to which computers are being put in medicine. It would well serve physicians or medical students with more serious interests and could serve as a text in developing a course on medical computing.

MARSDEN S. BLOIS, PhD, MD
*Professor and Chair, Section on Medical Information Science*
*University of California, San Francisco*

# Evaluation and Treatment of Smell Dysfunction

TERENCE M. DAVIDSON, MD; ALFREDO JALOWAYSKI, PhD; CLAIRE MURPHY, PhD, *and* ROBERT D. JACOBS, MD, *San Diego*

*We gave 63 patients with symptoms of smell dysfunction a full evaluation by age-adjusted olfactory threshold and odor identification testing, rhinomanometry, nasal cytology, nasal endoscopy, computed tomographic (CT) scan and a trial of medical treatment. CT scans were valuable for identifying ethmoid sinus disease and nasal endoscopy for inspecting olfactory epithelium. A trial of prednisone served as a diagnostic modality to identify correctable causes of smell dysfunction. Given that there are 2 million people in the United States with a smell dysfunction, that the average physician knows little about its diagnosis and treatment and that the psychosocial impact to an afflicted person is great, we urge a greater awareness of smell dysfunction, its diagnosis and its treatment.*

(Davidson TM, Jalowayski A, Murphy C, et al: Evaluation and treatment of smell dysfunction. West J Med 1987 Apr; 146:434-438)

The first scent that fills the air after an early morning spring rain, the bouquet of a vintage cabernet sauvignon, the aroma of fresh coffee brewing and the distinctive scent of a loved one are a few of the odors that complement our daily lives and trigger both physiologic and psychologic reactions. The secretion of saliva and stomach juices is a well-known response to the odors of food passing through our nose. In their ads, perfume companies exploit the relationship between fragrance and emotion. A recent article in the *National Geographic* (B. Gibbons, "The Intimate Sense of Smell," 1986; 170:324-361) summarizes well the important role that olfaction plays, and extrapolation makes it clear that the absence of olfaction is a real disability.

The lack of smell has never been considered a major disability, yet it is, and it can have very distressing effects. Spoiled foods cannot be detected before ingestion. Gas leaks or the smell of smoke during a fire are not detected until the situation becomes catastrophic. Smell dysfunction can reduce the overall quality of a person's life, lead to increased stress and depression and be a danger to those with whom a person lives and works. Olfactory loss is neither a new nor a rare disease. The most recent estimates by the National Institutes of Health are that 2 million American adults suffer disorders of taste and smell.[1] Nevertheless, few physicians have the knowledge and experience to adequately evaluate smell and taste disorders. Part of the reason physicians lack knowledge of olfactory disturbances is that the nasal innervation and the subsequent encoding system are poorly understood. Consequently, few physicians learn about the pathologic processes or teach olfactory perception in medical school. The result is that few specialists are prepared to handle the task of evaluating patients with olfactory loss because this requires added personnel, time, resources and expense.

An understanding of chemosensory dysfunctions begins with a definition of terms. Anosmia refers to the absence of the sense of smell. Hyposmia refers to diminished sensitivity to smell and dysosmia to a distortion of smell. Both phantosmia (smell of an odor for which there is no stimulus) and presbyosmia (hyposmia associated with aging) are important to remember. The absence of taste is termed ageusia, diminished sensitivity of taste is hypogeusia and dysgeusia is a distortion of taste.

It should be noted that among "normal persons" there is a wide range of olfactory acuity. Normal persons may have some degree of olfactory loss due to gender, smoking status or age. Women's olfactory acuity is superior to men's at all ages. Nonsmokers outperform smokers in olfactory testing. Doty showed that of persons older than 80 years, 80% evidenced major olfactory impairment with nearly 50% having anosmia.[2] Between 65 and 80 years of age, 60% had hyposmia and 25% anosmia.

A discussion of smell cannot exclude taste as they work together in the perception of flavor. Of the two senses, however, olfaction is by far the most important.

## Anatomy and Physiology

For an odor to be perceived, a substance must fulfill two requirements: it must be volatile at ambient temperature, and it must be soluble in fat solvents. Once such a molecule reaches the receptors located in the pigmented upper portion of the superior nasal cavity, it binds to and depolarizes the olfactory nerve receptors. Schiffman and co-workers reported that there are about 1 million bipolar olfactory nerve cells, with a turnover of about 30 days. The bipolar cells are grouped in bundles that penetrate the cribriform plate of the ethmoid bone and course centrally in the olfactory bulb, where they synapse with secondary olfactory neurons. Here they form small bushy masses known as glomeruli. From the olfactory bulb, projections of secondary neurons course to the primitive cortex, hippocampal formation and the pyriform lobe. Any one of these anatomic locations can produce olfactory dysfunction.[3]

From the Nasal Dysfunction Clinic (Dr Davidson); the Division of Head and Neck Surgery, the Department of Surgery (Drs Davidson, Murphy and Jacobs); the Pediatric Respiratory and Infectious Diseases Unit, the Department of Pediatrics (Dr Jalowayski), and the Department of Continuing Education (Dr Davidson), University of California, San Diego, Medical Center; the Department of Continuing Education, Veterans Administration Medical Center (Dr Davidson), and the Department of Psychology, San Diego State University (Dr Murphy), San Diego.

Reprint requests to Terence M. Davidson, MD, UCSD Medical Center, 225 Dickinson St (H-895), San Diego, CA 92103.

## Symptoms

Most patients who present with loss of smell report the change as a loss of taste, sometimes leading to a loss of appetite and weight loss, or, just as frequently, to increased food consumption and an associated weight gain. This seemingly paradoxic response is caused by a person eating more than normal in an attempt to "taste" what he or she is eating.

Most patients are seen initially by their primary physician and some are then referred to a head and neck surgeon. The patient initially disregards the changes, but ultimately seeks help as the disability persists and becomes an increasing annoyance. The absence of the usual pleasure of tasting foods becomes frustrating. Some patients may become the unfortunate victims of an explosion or fire resulting from their inability to detect leaking gas or smoke. Others are unable to detect rotten or spoiled food and may become the victims of food poisoning.

## Patients and Materials

The Nasal Dysfunction Clinic at the University of California, San Diego, during the year 1985 fully evaluated 63 patients with a primary complaint of the loss of the sense of smell. The evaluation included a detailed history, age-adjusted olfactory threshold and odor identification testing, rhinomanometry, nasal cytology and nasal endoscopy. Following the initial evaluation, patients were prescribed costeroids applied by nasal spray (two sniffs each nostril twice a day), zinc sulfate (440 mg three times a day), prednisone (60 mg a day for four days, then tapering doses for three days) and, if any element of infection was present, erythromycin (250 mg four times a day for six weeks). A computed tomographic (CT) scan of the anterior cranial fossa, nasal cavity and paranasal sinuses was done. Where appropriate, a patient was referred for psychiatric evaluation. Results of the CT scan, response to medicines and results of all laboratory tests were then assessed at six weeks. A diagnosis was made and appropriate recommendations given.

The olfactory testing is crucial to this evaluation. We use olfactory threshold and odor identification testing as developed by Cain and colleagues.[4] In a threshold task, patients seek to identify weak concentrations of the odorant *n*-butyl alcohol sniffed monorhinically from squeezable plastic bottles. The odorant is prepared in a series of dilutions beginning with 4% volume per volume in deionized water. Each of nine successive dilutions is a third the concentration of the preceding dilution. Two-alternative, forced-choice testing (alcohol solution versus a water blank) progresses from weaker to stronger concentrations. (Descending concentration series are generally avoided in olfactory threshold testing to minimize confounding by adaptation.) An incorrect choice, such as selection of the blank, leads to increased concentration on the next trial. Correct choices lead to presentation of the same concentration, to a criterion of four correct choices in a row. Two threshold determinations are made, one for each nostril.

The odor identification test consists of ten common odors, presented in random order, in small jars held under the nostrils. Patients close their eyes, sniff for about five seconds and then inspect the cue sheet provided. The cue sheet contains all ten odor names and ten distractor items. Testing proceeds from the right to left nostril until all items are presented once to each nostril. The patient is encouraged to guess when unsure and is provided with feedback about performance.

The maximum threshold score for each nostril is 50. Similarly, the maximum identification score for each nostril is 50. By summating the scores, an index of the patient's olfactory function is determined for each nostril. A score of 90 or 100 is considered normal, 60 to 80 mild hyposmia 40 to 60 moderate hyposmia, 20 to 40 severe hyposmia and 0 to 10 anosmia.

## Results

The best information can be gleaned from these data if reviewed by diagnostic category. The seven diagnostic categories are listed in Table 1. Olfaction was measured as described above. The response to steroid therapy was recorded as positive if a patient reported an early improvement in his or her sense of smell. Unless other specific therapy was instituted, the improvement on a steroid regimen was invariably transitory and served primarily as a diagnostic confirmation that the person had the potential to smell. For this study the CT scans were interpreted as normal or abnormal. The olfactory epithelium or superior nasal cavity (or both), if seen, yielded important diagnostic information. Rhinomanometry and nasal cytology were useful in confirming the diagnoses of nasal obstruction, infection and allergy. Interpretation of these tests is complex and is therefore reported in a separate publication.

### *Inflammatory Dysfunction*

Inflammatory disorders included infectious and allergic disease, and this category comprised the greatest number of patients. The test results are summarized in Table 2. Important observations are that men exceed women 2 to 1. Mean olfactory scores indicated severe hyposmia. These patients were unable to "taste" their foods and were unable to smell smoke, gas or spoiled food. Of 17 patients who took a one-week course of steroids, 100% noted some improvement in their ability to smell. Of the 13 patients who had a CT scan, 100% showed paranasal sinus disease. The single most important findings were mucosal thickening, air-fluid levels or opacification of the ethmoid sinuses.

TABLE 1.—*63 Patients With Smell Dysfunction*

| *Diagnostic Category* | *Patients, Number* | *%* |
|---|---|---|
| Inflammatory | 21 | 33 |
| Postviral | 20 | 32 |
| Trauma | 6 | 10 |
| Toxins | 7 | 11 |
| Congenital | 3 | 5 |
| Miscellaneous | 3 | 5 |
| Psychiatric | 3 | 5 |
| Total | 63 | 101 |

TABLE 2.—*Clinical Features of 21 Patients With Inflammatory Dysfunction*

| | |
|---|---|
| Age, yr | Mean 51; SD±12; range 27-74 |
| Male/female ratio | 14/7 |
| Olfactory scores | |
| Right nostril | Mean 31±32 (1 SD); range 0-90 |
| Left nostril | Mean 33±33 (1 SD); range 0-100 |
| Response to steroids | Improved 17; not improved 0 |
| CT scan findings | Abnormal 13; normal 0 |

CT=computed tomographic, SD=standard deviation

*Viral Dysfunction*

Findings in patients who lost their sense of smell after a viral illness are summarized in Table 3. Pertinent data included a male-to-female ratio of 1 to 4. Olfactory scores indicated severe hyposmia. Two patients noted an improved sense of smell on prednisone therapy and nine did not. One had an abnormal CT scan, and nine had a normal CT scan.

*Traumatic Dysfunction*

Findings associated with trauma-induced smell dysfunction are summarized in Table 4. Most patients were young men. Olfactory scores indicated anosmia in four patients and hyposmia in two. No improvement was noted with prednisone therapy, nor were abnormalities present on CT scans.

*Toxin Dysfunction*

Seven patients lost their sense of smell from toxin exposure. Relevant data appear in Table 5. The toxins responsible were ammonia (three cases), photodeveloping chemicals, hair dressing chemicals, liquid propane and a combination of acetone and cigar use, one case each. Olfactory scores indicated severe hyposmia. No patients responded favorably to the administration of corticosteroids, and none had abnormalities on a CT scan.

*Congenital Dysfunction*

Three patients were evaluated with congenital anosmia. All three scored 0 points on olfactory testing.

*Miscellaneous Dysfunction*

Three cases were categorized under miscellaneous dysfunction. One patient lost her smell after an ethmoidectomy. The surgical defect clearly involved the area of the olfactory epithelium. Two others lost their sense of smell following cerebrovascular accidents.

*Psychiatric Dysfunction*

The last category is psychiatric dysfunction. Three patients were studied. Two had normal smell in one nostril, but had hyposmia in the opposite nostril. One patient had true hyposmia, but also suffered a depressive illness.

*Endoscopic Rhinoscopy*

Endoscopic findings for all dysfunctions are reported in Table 6. Endoscopy was done with Storz glass rods (often called Hopkins rods). These are optically far superior to the flexible fiber-optic endoscopes. Endoscopy was carried out after phenylephrine (Neo-Synephrine) hydrochloride was administered for decongestion and tetracaine (Pontocaine) was given for anesthesia. The principal observations were that most patients with inflammatory dysfunctions had polyps and other inflammatory changes that prohibited observation of the olfactory epithelium. This is elaborated on in the discussion. With traumatic dysfunctions the dominant observation was that the olfactory epithelium appeared to be absent by visual inspection. Toxins also damaged the olfactory epithelium and, as expected, the olfactory epithelium was absent in the congenital cases seen.

## Discussion

One goal with patients complaining of a loss of their sense of smell is to make a diagnosis. If the diagnosis is inflammation, it is possible to improve the condition. If a brain tumor is discovered, neurosurgical consultation is required. If the loss is congenital or acquired and is permanent, the patient needs a careful explanation and appropriate rehabilitation.

Several observations from this experience are worth noting.

*Inflammatory Dysfunction*

Inflammatory causes are easily identified. Often a patient complains of a fluctuating loss, which essentially clinches the diagnosis. The majority have abnormal nasal cytology and abnormal CT scans. The most common x-ray film abnormality is opacified cells in the ethmoid sinuses. Generally, inspection of the olfactory epithelium is obstructed by polyps or intranasal mucosal inflammation.

Recovery of the sense of smell on prednisone therapy im-

TABLE 3.—*Clinical Features of 20 Patients With Postviral Dysfunction*

| | |
|---|---|
| Age, yr | Mean 60; SD±14; range 39-89 |
| Male/female ratio | 4/16 |
| Olfactory scores | |
| Right nostril | Mean 36±34 (1 SD); range 0-90 |
| Left nostril | Mean 29±28 (1 SD); range 0-90 |
| Response to steroids | Improved 2; not improved 9 |
| CT scan findings | Abnormal 1; normal 9 |

CT=computed tomographic, SD=standard deviation

TABLE 4.—*Clinical Features of 6 Patients With Traumatic Dysfunction*

| | |
|---|---|
| Age, yr | Mean 33; SD±8; range 21-42 |
| Male/female ratio | 5/1 |
| Olfactory scores | |
| Right nostril | Mean 10±17 (1 SD); range 0-40 |
| Left nostril | Mean 17±20 (1 SD); range 0-50 |
| Response to steroids | Improved 0; not improved 4 |
| CT scan findings | Abnormal 0; normal 5 |

CT=computed tomographic, SO=standard deviation

TABLE 5.—*Clinical Features of 7 Patients With Toxin Dysfunction*

| | |
|---|---|
| Age, yr | Mean 54; SD±12; range 34-67 |
| Male/female ratio | 3/4 |
| Olfactory scores | |
| Right nostril | Mean 36±33 (1 SD); range 0-80 |
| Left nostril | Mean 27±30 (1 SD); range 0-80 |
| Response to steroids | Improved 0; not improved 3 |
| CT scan findings | Abnormal 0; normal 5 |

CT=computed tomographic, SD=standard deviation

TABLE 6.—*Endoscopic Observations of Olfactory Epithelium (N=63)*

| *Dysfunction* | *Normal* | *White* | *Absent* | *Polypoid* | *Not Seen* |
|---|---|---|---|---|---|
| Inflammatory | 2 | 0 | 0 | 2 | 17 |
| Postviral | 0 | 13 | 4 | 0 | 3 |
| Trauma | 1 | 0 | 4 | .. | 1 |
| Toxins | 1 | 2 | 2 | .. | 1 |
| Congenital | .. | .. | 3 | .. | .. |
| Miscellaneous | .. | .. | 1 | .. | 2 |
| Psychiatric | .. | .. | 1 | .. | 3 |

plies there is a potential to smell and appears to be pathognomonic for inflammatory nasal disease.

*Viral Dysfunction*

Occasionally a viral illness results in a loss of the sense of smell. Whereas men predominated in the inflammatory category cases by a factor of 2 to 1, women exceeded in cases of viral-induced dysfunction by 4 to 1. Some patients reported the loss of smell to be coincident with an upper respiratory tract illness or a flulike syndrome, while others had difficulty making such an association. One notable case was a woman who had a "cold" and lost her sense of smell. Her husband contracted the same "cold" a week or so later and he, too, lost his sense of smell. Rhinomanometry, nasal cytology and CT scans were all essentially normal in the patients with a diagnosis of postviral hyposmia. While nine patients had no response to steroid therapy, two did note a slight improvement. To what degree this represented a concomitant inflammatory condition or some temporary recovery is unclear.

The most interesting observation was seen at nasal endoscopy. The olfactory epithelium was replaced with a white strip of tissue. One physician compared this with the findings in cases of optic atrophy. On closer inspection our impression was that this represented scar tissue and correlated very strongly with a postviral cause. The appearance was definitely different from that seen with traumatic or congenital dysfunctions wherein the olfactory epithelium appeared to be completely missing and replaced by a thin layer of mucosa. Whether this observation was exclusive to or only strongly suggestive of postviral dysfunction is yet unclear. More and more, our impression is that the white scarred tissue strongly suggests a postviral smell disorder.

*Traumatic Dysfunction*

The traumatic disorders predominated in younger men. Olfactory scores were lower than those seen in patients with the inflammatory and postviral causes. Rhinomanometry, nasal cytology and CT scans were normal. In no cases was a fracture in or near the cribriform plate noted. Endoscopy revealed no tissue resembling olfactory epithelium. The only trauma patient who had any olfactory epithelium was a 28-year-old man with olfactory scores of 40 and 50, indicating moderate hyposmia. At endoscopy the olfactory epithelium was normal, appearing raised and yellow.

*Toxin Dysfunction*

The cases of toxin-induced dysfunction were fascinating. Some cases were very clear such as one man who purchased a sandwich at a fast-foods market, bit into the sandwich and cracked an ammonia-containing cylinder like those used for arousing fainting patients. He suffered a severe nasopharyngeal and intranasal burn, lost his sense of smell and never regained it. Olfactory scores averaged around 30, but there was a large standard deviation, ranging from 0 to 80. Rhinomanometry and nasal cytology were normal. CT scans were also normal, and none of these patients reported improvement on prednisone therapy. Endoscopic findings were significant. In two patients, no olfactory epithelium was observed. Two patients had the white scarring seen with postviral dysfunction. Whether these represented postviral dysfunctions or an alternate method of scarring is difficult to say. If the white appearance was indeed scar tissue, toxic destruction would be consistent with such findings. One man with olfactory scores of 70 to 80, with heavy exposure to acetone and a history of smoking five to six cigars a day, had normal-appearing olfactory epithelium. Another person exposed to photodeveloping chemicals and with scores of 60 and 80 had a yellow, flattened epithelium with areas of scarring across it.

*Congenital Dysfunction*

The cases of congenital losses were straightforward. Olfactory scores in all three patients were 0 in both nostrils. In all cases the olfactory epithelium appeared to be absent and replaced by a thin mucosa. Rhinomanometry, nasal cytology and CT scans were normal. Most interesting was their history. These patients had never smelled and hence did not consider it a major dysfunction. Food was attractive to them and they tended to focus on sensations such as salt, sweet, sour, bitter, temperature and feel. This was in strong contrast to those whose chemosensory loss occurred later in life. For those patients the loss of smell was a major loss. This was particularly so for persons for whom cooking was a major part of their lives. One woman's tearful description of not being able to smell her own Christmas dinner was frankly tragic. Some patients lost their appetite and lost weight. Others reported eating too much, hoping with each bite for some "taste" to come through.

Discussing the loss of the sense of smell has been greatly hampered by the English language. The major chemosensory input from food is smell. This is most commonly called taste, but has little to do with the chemosensory tastes of sweet, sour, bitter and salt. It would be better if food were described differently. Certainly it has a characteristic appearance. Often we discuss its temperature and occasionally we note its lack or excess of sweet, sour, bitter or salt. We seldom note this if all is well. We only note aroma if the food is still on the plate and almost never take a bite and exclaim that the food smells great. For purposes of discussion in the clinic, we refer to the overall gestalt of food as its flavor and reserve the word taste for the four known tastes.

*Miscellaneous Dysfunction*

The miscellaneous category included one patient who clearly lost her sense of smell after an intranasal ethmoidectomy. Nasal endoscopy confirmed that the surgeon had operated medial to the attachment of the middle turbinate bilaterally and had removed virtually all of the olfactory epithelium.

The other two patients appear to have lost their sense of smell following cerebrovascular accidents. This was difficult to confirm. One had abnormal ethmoid sinuses on CT scan, but as he did not respond to antibiotic or prednisone therapy, he did not belong in the inflammatory category. Various drugs have allegedly interfered with the sense of smell. Both patients had taken a variety of medicines, and perhaps this offers an alternate cause.

*Psychiatric Dysfunction*

The last category is psychiatric. One patient had olfactory scores of 100 and 60, the other 80 and 100. The remainder of their evaluation was normal and certainly both had significant psychiatric difficulties. The third patient was depressed, associated with retirement and a major financial error and loss. His olfactory scores were 20 and 30, and the remainder of his evaluation was normal. Psychotherapy partially resolved his depression, but did not subjectively alter his sense of smell. One patient in this category with normal smell did not have olfactory-looking epithelium at endoscopy. Given the normal olfactory scores, this was most likely an inadequate examina-

tion. There is a definite decrease in the olfactory threshold with age. The olfactory scores are corrected for this, but this patient represents an extreme of this phenomenon, which we refer to as presbyosmia.

In this overall series of 63 patients, none identified any benefit from zinc sulfate therapy. Two patients whose workups were not complete and therefore were not included in the study did report by telephone that they felt better after taking zinc. To what degree this represented improved olfaction and to what degree the improvement was related solely to other effects of zinc is undetermined.

Anosmia has received far less attention than have other sensory defects such as blindness and deafness. Hence, little has been done in the field of rehabilitation. The most worrisome problems are the inability to smell smoke, gas or spoiled food. Patients are advised to place smoke detectors in the kitchen, by the fireplace, near all other places where fire might occur and in all rooms in which they nap or sleep.

They are advised not to keep gasoline in the garage or in sheds and certainly never to light a match wherever there might be gas. For those using propane or natural gas, industrial grade gas detectors are recommended. Propane gas and gasoline are heavier than air so the detectors must be mounted at floor level. Natural gas is lighter than air and requires ceiling-mounted gas sensors. The best referral source for gas detectors is a marine electronics store because various gas detectors are used in most larger boats.

Persons with anosmia are unable to detect spoiled food. If they live with other people they should *always* ask someone with a normal sense of smell to sniff leftovers and other foods likely to be spoiled. If they live alone, they must develop a rigid program for discarding leftover food.

The most difficult problem for these persons is rehabilitating their eating pleasures. Attention must be diverted from smell to the other senses. Appearance, temperature, texture and taste must be highlighted. Many patients have been able to season with nasal and oral trigeminal stimulants. These include horseradish, capsicum, mustard, ginger, clove, cinnamon, peppermint, spearmint, pepper and pimento. Mexican foods and Indian dishes are often appreciated for their spices and hot sauces, which are stimulating.

Salt ideally should not become a desired taste because these persons might consume it heavily. Also, for those finding themselves overindulging in search of flavor, weight control must be taught.

#### REFERENCES

1. Schiffman SS: Taste and smell in disease. N Engl J Med 1983; 308 (Pt I):1275-1279; (Pt II):1337-1343

2. Doty RL: A review of olfactory dysfunctions in man. Am J Otolaryngol 1979; 1:57-79

3. Schiffman S, Orlandi M, Erickson RP: Changes in taste and smell with age: Biological aspects, *In* Ordy JM, Brizzee K (Eds): Sensory Systems and Communication in the Elderly. (Aging Series, Vol 10.) New York, Raven Press, 1979, pp 247-268

4. Cain WS, Gent J, Catalanotto F, et al: Clinical evaluation of olfaction. Am J Otolaryngol 1983; 4:252-256

# Absence of HIV Antibody Among Dental Professionals Exposed to Infected Patients

NEIL M. FLYNN, MD; STEPHEN M. POLLET, MD; JAMES R. VAN HORNE; RANVEIG ELVEBAKK, MD; SCOTT D. HARPER, *and* JAMES R. CARLSON, PhD, *Davis, California*

*Dental professionals have relatively frequent skin contact with saliva and small amounts of blood of patients infected with the human immunodeficiency virus (HIV). Despite this exposure, none of 255 dentists, hygienists and chairside assistants had the antibody to HIV following an estimated 189 or more exposures. These data provide further evidence that casual contact with the saliva of HIV-infected persons, such as may occur in households, the workplace or in public places, is unlikely to result in transmission of HIV to uninfected persons. Because of the small sample size in this study, however, and the relatively high frequency of exposure of HIV-infected patients that we found, we recommend that dental care professionals increase their use of disposable gloves and adhere to the Centers for Disease Control's guidelines for infection control practices for dentistry until more is known about the transmission of this virus.*

(Flynn NM, Pollet SM, Van Horne JR, et al: Absence of HIV antibody among dental professionals exposed to infected patients. West J Med 1987 Apr; 146:439-442)

Transmission of the human immunodeficiency virus (HIV) occurs through sexual intercourse, needle and syringe sharing by intravenous drug users, transfusion of blood or blood products containing the virus and vertical transmission from mother to infant.[1] A few incidents of transmission to health care professionals through accidental parenteral exposure to HIV-infected material have been reported.[2-10] Currently the risk of transmission to health professionals is calculated to be about 1.6% or less per parenteral or mucous membrane exposure (95% confidence upper limit).[7] Each year the acquired immunodeficiency syndrome (AIDS) develops in as many as 5% to 7% of HIV-infected persons.[11]

Occupational exposure of dental care professionals predisposes them to blood- and saliva-borne infections, as shown by a relatively high prevalence of antibodies to the hepatitis B virus (HBV).[12] In one study, 29% of oral surgeons tested had antibody to HBV.[13] We investigated the possibility that HIV, also present in blood and saliva, can be transmitted to dental professionals in a manner analogous to HBV.[14-16]

## Subjects and Methods

We attempted to contact all dentists practicing in the Sacramento (California) metropolitan area and in a nearby university community, Davis. They were asked to participate in a serologic survey to detect evidence of previous HIV infection. We used no exclusion criteria. Between April and July 1985, one or more of us visited the offices of dentists who agreed to participate in the study. Informed consent, approved by the Human Subjects Research Committee of the University of California, Davis, was obtained from each participant. A serum specimen was then obtained from the dentists and their paradental employees (dental hygienists and chairside assistants).

The subjects were asked to estimate the number of contaminated instrument puncture wounds they experienced per month, the percentage of procedures in which they wore gloves and the percentage of their patients who were homosexual men, intravenous drug users or persons with hemophilia. A follow-up questionnaire was administered three months later to determine whether this study had had an effect on gloving practices.

Testing for the HIV antibody was done using the sensitive enzyme-linked immunosorbent assay (ELISA) method for screening and the more specific Western blot and immunofluorescent assay (IFA) techniques for confirming positive results.[17]

We surveyed HIV antibody-positive patients attending the University of California Davis Clinic for AIDS and Related Disorders regarding the number of visits they had made to dentists over the previous two years and the identities of these dentists. We cross-checked these dentists with those who participated in the serosurvey and obtained serum specimens from three additional dentists who had not participated in the initial survey, but who had been identified by our patients.

An estimate of the number of persons in the Sacramento area who have been previously infected with HIV was based on crude extrapolations from the incidence and prevalence of AIDS in Sacramento County and estimated ratios of infected persons to AIDS cases.[18,19]

From the Division of General Medicine, Departments of Internal Medicine (Dr Flynn, Dr Pollet, Mr Van Horne, Dr Elvebakk and Mr Harper) and Pathology (Dr Carlson), University of California, Davis, School of Medicine.

This study was supported by a grant from the University of California Task Force on AIDS.

Reprint requests to Neil M. Flynn, MD, Division of General Medicine, 3120 Primary Care Bldg, 2221 Stockton Blvd, Sacramento, CA 95817.

ABBREVIATIONS USED IN TEXT

AIDS = acquired immunodeficiency syndrome
HBV = hepatitis B virus
HIV = human immunodeficiency virus
IFA = immunofluorescent assay

## Results

We tested 89 dentists, 36 dental hygienists and 130 chairside assistants. None of these 255 dental care professionals showed evidence of HIV infection by Western blot or IFA techniques.

Of the participating dentists, 41 practice in the city of Sacramento (9% of Sacramento dentists), 31 in surrounding communities (37% of dentists) and 17 in the city of Davis (67%). Most of the paradental employees in these dentists' offices participated in the study.

To document the number of visits by HIV-infected patients to our dental cohort, we contacted 48 HIV antibody-positive patients seen in the Clinic for AIDS and Related Disorders. Of these, 39 had visited a dentist in the past two years, for a total of 107 visits, and 9 had not visited a dentist (an average of 1.1 visits per patient per year). In all, 17 of the patients had seen 13 of the dentists enrolled in this study for a total of 55 visits over the previous two years. At least two dental professionals were exposed at each visit, resulting in 110 documented exposures of dental cohort subjects by patients probably infected with HIV at the time of the visit.

TABLE 1.—*Dental Professionals Who Have Accidental Puncture Wounds Per Month, by Job Description*

| | Number of Puncture Wounds Per Month | | | |
|---|---|---|---|---|
| *Dental Care Professionals* | *0 to 1, Percent* | *2 to 5, Percent* | *6 to 15, Percent* | *>15, Percent* |
| Dentists, N=89 | 68 | 13 | 16 | 3 |
| Chairside Assistants, N=130 | 51 | 22 | 21 | 6 |
| Hygienists, N=36 | 63 | 8 | 18 | 11 |
| Total, N=255 | 58 | 17 | 19 | 6 |

Results of the initial questionnaire showed that 18% of dentists estimated that more than 10% of their patient population were members of groups at high risk for HIV infection. Accidental skin punctures with contaminated instruments were common among the dental professionals studied: 25% of participants indicated that they have more than five puncture wounds per month while doing dental procedures, and 6% indicated that they have more than 15 punctures per month (Table 1). We documented no instances of punctures involving patients known or suspected to be infected with HIV.

Most dentists surveyed rarely wear gloves while doing procedures. Hygienists use gloves more frequently than dentists or chairside assistants ($P \leq .05$). In all, 53% of the hygienists surveyed said that they wear gloves during all procedures (Table 2).

A total of 109 dental professionals enrolled in this study returned a follow-up questionnaire regarding changes in gloving habits as a result of participating in the study. Of these, 35 said that they had increased their use of gloves during dental procedures as a result of this study, an additional 7 already wore gloves in more than 90% of procedures before participating in the study and 67 reported no change in their gloving habits.

Based on the apparent frequency of dental visits by HIV-infected persons and the number of them estimated to reside in the community, we calculated the number of exposures experienced by our dental cohort personnel. Moss has estimated that the ratio of infected persons to total reported cases of AIDS in a community is approximately 30:1.[18] Sivak and Wormser, on the other hand, have estimated that the ratio of HIV-infected persons to living AIDS cases may be as high as 300:1, based on observations of intravenous drug users and persons with hemophilia.[19]

Between March 1983 and June 1985, there were 22 cases of AIDS reported in Sacramento County. In June 1985 there were 20 known county residents alive with a diagnosis of AIDS, some of whose cases had not yet been reported to the Sacramento County Health Department. Based on the calculations in Table 3, we estimate that there may have been

TABLE 2.—*Gloving by Dental Professionals, by Job Description—Percent Who Wore Gloves for Indicated Percent of Procedures*

| | Procedures in Which Gloves Worn, Percent | | | | | |
|---|---|---|---|---|---|---|
| | *0* | *1 to 10* | *11 to 20* | *21 to 60* | *61 to 99* | *100* |
| *Professionals, Percent* | | | | | | |
| Dentists, N=89 | 23 | 52 | 6 | 12 | 4 | 3 |
| Chairside Assistants, N=130 | 46 | 28 | 4 | 8 | 5 | 9 |
| Hygienists, N=36 | 10 | 24 | 0 | 8 | 5 | 53 |
| Total, N=255 | 34 | 35 | 5 | 8 | 5 | 13 |

TABLE 3.—*Estimated Number of Exposures of Dental Cohort Personnel to Persons Infected With the Human Immunodeficiency Virus (HIV)*

Estimate A*

$$\frac{30 \text{ infected persons}}{\text{reported case of AIDS}} \times 22 \text{ reported cases} \times \frac{1.1 \text{ visits}}{\text{year}} \times \frac{2 \text{ professionals exposed}}{\text{dental visit}} = 1{,}452 \text{ exposures/year}$$

Estimate B†

$$\frac{300 \text{ HIV-infected persons}}{\text{living case of AIDS}} \times 20 \text{ living cases} \times \frac{1.1 \text{ visits}}{\text{year}} \times \frac{2 \text{ professionals exposed}}{\text{dental visit}} = 13{,}200 \text{ exposures/year}$$

AIDS=acquired immunodeficiency syndrome

*Using ratio of 30:1 calculated by Moss.[18]
†Using ratio of 300:1 calculated by Sivak and Wormser.[19]

between 1,452 and 13,200 exposures of Sacramento County dental personnel to HIV-infected persons in 1985.

If HIV-infected persons visited dentists more or less randomly distributed throughout Sacramento County, we would expect the 72 county dentists enrolled in our cohort to have experienced 13% of these visits, or about 189 (low estimate) to 1,716 (high estimate) exposures.

## Discussion

Despite a relatively large number of calculated and 110 documented exposures to patients who were probably infected with HIV at the time of the exposure, no participants in this study had antibody to the virus by Western blot or IFA testing. The cohort we studied appears to be at relatively low risk for infection with HIV. There are several possible explanations for these findings. First, our sample size may be too small to detect significant risk. Actual risk based on our sample size could be as low as 0% or as high as 2.7% per exposure (95% confidence limits).

Second, the probability of an accidental puncture wound occurring with any individual patient is relatively small; therefore, dental professionals probably rarely have blood-to-blood contact in the form of accidental puncture wounds while providing care to HIV-infected patients. On the other hand, most of the professionals we questioned do not wear gloves, have blood-to-skin contact with many patients and have the ordinary number of skin abrasions, small cuts and dermatitis that might provide a portal of entry for HIV-infected blood. Likewise, dentists cannot readily determine whether a particular patient is an asymptomatic carrier of HIV to reduce their risk of exposure by wearing gloves and taking special precautions with such patients. Many patients we queried do not tell their dentist of their HIV-antibody status because of the fear of rejection.

Third, the probability of transmission of HIV, even following needlestick exposure, appears to be low.[2-10] Four cases of AIDS,[2,3] three incidents of HIV-antibody positivity[4-7] and four incidents of HIV-antibody seroconversion[8-10] have been reported in health care workers. The four cases of AIDS occurred relatively early in the AIDS epidemic, and the accuracy of data regarding possible sexual exposure and intravenous drug use by these persons could not be verified.[2] No further cases of AIDS have been reported in health care workers lacking known risk factors for acquiring the HIV, suggesting that this early report should be viewed with skepticism. McCray has estimated that the risk of transmission of HIV to health care workers following a parenteral exposure to infected blood is 0.72% (upper bound of the 95% confidence interval is 2.24%).[7] Hepatitis B and cryptococcosis have been transmitted as a result of needlesticks sustained by health care workers caring for AIDS patients, without concomitant transmission of the HIV.[20,21] It appears that HIV is rarely transmitted by the type of accidental exposures that occur between infected patients and health care professionals because of the small amount of blood transferred by needlestick and the low number of viral particles estimated to be present in the peripheral blood of HIV-infected persons (approximately 25,000 per ml serum).[22]

Fourth, there may be degrees of HIV viremia, or infectivity of individual strains of the virus. Numbers and infectivity of virus could vary according to the duration of infection, individual donor-host factors and properties of the virus. Finally, a recipient's susceptibility to infection after inoculation with the virus may vary.

We did this study to detect transmission of HIV from patient carriers to dental care professionals, but there is also the theoretic possibility of transmission from a dental or medical professional carrier to his or her patients, analogous to transmission of hepatitis B from a hepatitis B e-antigen-carrier professional to patients.[23] This possibility appears to be exceedingly unlikely because of the low numbers of HIV circulating in blood in comparison to the enormous numbers of particles in patients with hepatitis B e-antigen-positive HBV viremia ($N = \geq 10^8$ infectious particles per ml of serum).[24] Health care professionals who are known to be HIV carriers or who are members of a high-risk group for infection with the virus and who do procedures on patients in which transfer of the operator's blood to the patient may occur should take extraordinary precautions to protect their patients until more is known about transmissibility of the virus. There is also a theoretic possibility of transfer of the virus from one infected patient to another patient on the hands or contaminated gloves of professionals or on contaminated instruments such as parts of a drilling apparatus that have not been disinfected adequately between patients. Because this has not been reported to occur with the hepatitis B virus, it is unlikely that HIV will be transmitted in this way.

Despite the negative findings in this study, we recommend that dental professionals follow the guidelines from the Centers for Disease Control contained in "Recommended Infection Control Practices for Dentistry" to reduce exposure to all blood- and saliva-borne infections.[25] In the case of HIV, we estimate 2.2 million or more exposures of dental care professionals to HIV-infected persons will occur this year; we base this on estimates by the Centers for Disease Control of the number of infected persons in the United States (1 million or more) and the observed rate of dental visits by our clinic patients.[26] It is reassuring that no dental professionals have been reported to have HIV infection from professional contact despite this apparently large number of exposures.

This study also provides further evidence that casual contact with the saliva of HIV-infected persons, such as may occur within households, in the workplace or in public places, is extremely unlikely to result in transmission of the virus to uninfected persons.

In summary, this study provides evidence that transmission of HIV does not readily occur from infected patients to dental care professionals who carry out procedures on these patients. It also shows that professional contact between dental care professionals and those infected with HIV is frequent. A larger study conducted in an area of higher prevalence of HIV infection, such as San Francisco or New York City, is needed to better estimate the risk of transmission of the virus by this route.

### REFERENCES

1. Centers for Disease Control: Provisional Public Health Service inter-agency recommendations for screening donated blood and plasma for antibody to the virus causing AIDS. MMWR 1985; 34:1-5

2. Centers for Disease Control: An evaluation of the acquired immunodeficiency syndrome (AIDS) reported in health-care personnel—United States. MMWR 1983; 32:358-360

3. Belani A, Dunning R, Dutta D, et al: AIDS in a hospital worker (Letter). Lancet 1984; 1:676

4. Needlestick transmission of HTLV-III from a patient infected in Africa. Lancet 1984; 2:1376-1377

5. Centers for Disease Control: Update: Evaluation of human T-lymphotropic virus type III/lymphadenopathy-associated virus infection in health-care personnel—United States. MMWR 1985; 34:575-578

6. Weiss SH, Rechtman DJ, Landesman S, et al: HTLV-III infection among health care workers. JAMA 1985; 254:2089-2093

7. McCray E and the Cooperative Needlestick Surveillance Group, CDC: Occupational risk of the acquired immunodeficiency syndrome among health care workers. N Engl J Med 1986; 314:1127-1132

8. Centers for Disease Control: Apparent transmission of human T-lymphotropic virus type III/lymphadenopathy-associated virus from a child to a mother providing health care. MMWR 1986; 35:76-79

9. Stricof RL, Morse DL: HTLV-III/LAV seroconversion following a deep intramuscular needlestick injury (Letter). N Engl J Med 1986; 314:1115

10. Oksenhendler E, Harzic M, Le Roux JM, et al: HIV infection with seroconversion after a superficial needlestick injury to the finger (Letter). N Engl J Med 1986; 315:582

11. Goedert JJ, Biggar RJ, Weiss SH, et al: Three-year incidence of AIDS in five cohorts of HTLV-III-infected risk group members. Science 1986; 231:992-995

12. West DJ: The risk of hepatitis B infection among health professionals in the United States. Am J Med Sci 1984; 287:26-33

13. Council on Dental Therapeutics: Type B (serum) hepatitis and dental practice. J Am Dent Assoc 1976; 92:153-159

14. Scott RM, Snitbhan R, Bancroft WH, et al: Experimental transmission of hepatitis B virus by semen and saliva. J Infect Dis 1980; 142:67-71

15. Feorino PM, Kalyanaraman VS, Haverkos HW, et al: Lymphadenopathy associated virus infection of a blood donor-recipient pair with acquired immunodeficiency syndrome. Science 1984; 225:69-72

16. Groopman JE, Salahuddin SZ, Sarngadharan MG, et al: HTLV-III in saliva of people with AIDS-related complex and healthy homosexual men at risk for AIDS. Science 1984; 226:447-449

17. Carlson JR, Bryant ML, Hinrichs SH, et al: AIDS serology testing in low- and high-risk groups. JAMA 1985; 253:3405-3408

18. Moss AR: What proportion of HTLV-III antibody positives will proceed to AIDS? (Letter). Lancet 1985; 2:223

19. Sivak SL, Wormser GP: How common is HTLV III infection in the United States? (Letter). N Engl J Med 1985; 313:1352

20. Gerberding JL, Hopewell PC, Kaminsky LS, et al: Transmission of hepatitis B without transmission of AIDS by accidental needlestick (Letter). N Engl J Med 1985; 312:56-57

21. Glaser JB, Garden A: Inoculation of cryptococcosis without transmission of the acquired immunodeficiency syndrome (Letter). N Engl J Med 1985; 313:266

22. Levy JA, Kaminsky LS, Morrow WJW, et al: Infection by the retrovirus associated with the acquired immunodeficiency syndrome. Ann Intern Med 1985; 103;694-699

23. Goodwin D, Fannin SL, McCracken BB: An oral-surgeon related hepatitis-B outbreak. Calif Morbidity 1976 Apr 16

24. Shikata T, Karasawa T, Abe K, et al: Hepatitis B e antigen and infectivity of hepatitis B virus. J Infect Dis 1977; 136:571-576

25. Centers for Disease Control: Recommended infection control practices for dentistry. MMWR 1986; 35:237-242

26. Berkeley Springs Conference on AIDS, West Virginia, 1986, Sponsored by US Public Health Service. Reported in: Chilling predictions of future of AIDS. The Nation's Health 1986 July, p 14

# Laboratory Evaluation of Anemia

RALPH O. WALLERSTEIN, Jr, MD, *San Francisco*

*The laboratory evaluation of anemia begins with a complete blood count and reticulocyte count. The anemia is then categorized as microcytic, macrocytic or normocytic, with or without reticulocytosis. Examination of the peripheral smear and a small number of specific tests confirm the diagnosis. The serum iron level, total iron-binding capacity, serum ferritin level and hemoglobin electrophoresis generally separate the microcytic anemias. The erythrocyte size-distribution width may be particularly helpful in distinguishing iron deficiency from thalassemia minor. Significant changes have occurred in the laboratory evaluation of macrocytic anemia, and a new syndrome of nitrous oxide-induced megaloblastosis and neurologic dysfunction has been recognized. A suggested approach to the hemolytic anemias includes using the micro-Coombs' test and ektacytometry. Finally, a number of causes have been identified for normocytic anemia without reticulocytosis, including normocytic megaloblastic anemia and the acquired immunodeficiency syndrome.*

(Wallerstein RO Jr: Laboratory evaluation of anemia. West J Med 1987 Apr; 146:443-451)

The clinical evaluation of anemia is a common problem in medicine. During the past decade, advances have occurred in the understanding of the pathophysiology of several specific causes of anemia, and progress has been made in technology and the procedures used to do several common clinical tests. In this article I will review the current laboratory evaluation of anemia.

The use of electronic cell counters to do complete blood counts has become virtually universal. Most of them directly and precisely measure the mean corpuscular volume (MCV), hemoglobin concentrations and erythrocyte count, but only calculate the hematocrit, the mean corpuscular hemoglobin level and the mean corpuscular hemoglobin concentration. These calculations may not always be accurate, especially if the erythrocytes are deformed, as in sickle cell anemia. Because the hematocrit is calculated from the MCV and erythrocyte count, the artifact of plasma trapping does not occur as it does in a spun hematocrit. Plasma trapping is particularly prominent when the erythrocytes are misshapen or rigid, as in iron deficiency or sickle cell disease. One needs to be aware of this because if an initial hematocrit is done by microcentrifuge in the emergency department, a subsequent hematocrit in the central laboratory done by electronic counter may be much lower, when no true fall in hematocrit has occurred. Because the hemoglobin concentration is directly measured and the hematocrit calculated, the hemoglobin today is a more accurate and reproducible assessment of anemia.[1] A new piece of information, now frequently available, is a visual histogram of the distribution of erythrocyte sizes and a calculation of the coefficient of variation of the erythrocyte size expressed as the erythrocyte, or red blood cell, size-distribution width (RDW). Both of these are based on the electronic counting and sizing of $10^5$ cells. The RDW, a measure of dispersion, corresponds to the clinical assessment of anisocytosis—not poikilocytosis—but is more sensitive than visual observation. When iron, vitamin $B_{12}$ or folate become limiting, erythrocytes of abnormal size are produced, the visual histogram widens and the RDW increases. Occasionally two populations of cells may be observed in the histogram and, after therapy, one may be able to observe an increase in the normal size population and a decrease in the abnormal population. The ability to detect two populations, such as patients with sideroblastic anemia or those with transfusions, is limited by the height of the second population (must be more than 5%) and its separation by an observable trough from the main population.[2] The program used to calculate the RDW varies from instrument to instrument, and, in some cases, the histogram may contain information not conveyed by the RDW. In general, the RDW is increased with qualitative defects, such as lack of iron, vitamin $B_{12}$ or folic acid, but is normal in quantitative defects such as hypoplastic anemias.[3] An increased RDW may be particularly helpful in distinguishing between iron deficiency and thalassemia minor.[4] When the MCV is normal but the RDW is increased, early iron, folate or vitamin $B_{12}$ deficiency or a dimorphic anemia such as iron and folate deficiency may be looked for. The RDW, however, has not been rigorously tested in a prospective fashion nor outside of institutions with an interest in the area; its sensitivity and specificity in widespread clinical practice are not as yet established, and at present it does not replace the traditional evaluation. Anemias have been classified clinically by MCV for many years. The precise determination of MCV by the current machines makes the limited differential diagnosis of microcytic and macrocytic indices a useful approach.

## Microcytic Anemias

The causes of an MCV of less than 80 cu microns are shown in Table 1.

In the vast majority of cases, microcytic indices are either iron deficiency or thalassemia. They usually can be distin-

From the Departments of Medicine and Laboratory Medicine, University of California, San Francisco, School of Medicine, San Francisco.
Reprint requests to Ralph O. Wallerstein, Jr, MD, 3838 California St, Suite 707, San Francisco, CA 94118-1560.

ABBREVIATIONS USED IN TEXT

AIDS = acquired immunodeficiency syndrome
ARC = AIDS-related complex
DIC = disseminated intravascular coagulation
EDTA = ethylenediaminetetraacetic acid
FEP = free erythrocyte protoporphyrin
G6PD = glucose-6-phosphate dehydrogenase
Hb = hemoglobin
Ig = immunoglobulin
LDH = lactic dehydrogenase
MCV = mean corpuscular volume
RDW = red blood cell size-distribution width
TIBC = total iron-binding capacity

guished easily by looking at the MCV, erythrocyte count, hemoglobin level and RDW. In iron deficiency, the progression of laboratory abnormalities is a loss of stainable bone marrow iron, a decrease in the serum ferritin level, a decrease in the serum iron content and an increase in total iron-binding capacity, anemia, a decrease in the MCV, increasing poikilocytosis and hypochromia. Generally, the MCV does not fall below 80 cu microns until the hemoglobin level is less than 10 grams per dl. The erythrocyte count decreases and the RDW increases early. The fall in the erythrocyte count is less than the fall in hemoglobin, and it is unusual to find an erythrocyte count below 2.5 million per $\mu$l in a case of pure iron deficiency anemia. In thalassemia minor, although there is variation in cell shape and the cells are small, the variation in size is no more than normal and the RDW is normal. The body attempts to compensate for the anemia with an increase in erythrocytes. Thus, in a patient with microcytic anemia, if the erythrocyte count is normal or increased, thalassemia is the most likely diagnosis. If the hemoglobin level is greater than 10 grams per dl but the MCV is less than 75 cu microns, thalassemia is also more likely. Clinicians have used two formulas in an attempt to quantitate these relationships: (1) the Mentzer index (MCV/erythrocyte count) that, if less than 13, favors thalassemia minor and, if greater than 13, favors iron deficiency; and (2) the discriminant function (DF′) of England and Fraser (DF′ = MCV − [hemoglobin $\times$ 5] − erythrocyte count − 3.4) where a negative number indicates thalassemia and a positive number iron deficiency. When the two formulas were compared with the RDW, however, the RDW proved to be much more accurate in correctly distinguishing thalassemia minor from iron deficiency.[4] At present, even the RDW does not replace a traditional evaluation, and the diagnosis must be confirmed.

A number of laboratory techniques exist to evaluate iron stores. To be diagnostic of iron deficiency, one needs to have an iron value of less than 60 $\mu$g per dl and a total iron-binding capacity (TIBC) of greater than 350 $\mu$g per dl. If the TIBC is reduced, one cannot make a diagnosis of iron deficiency—no matter how low the saturation—although iron deficiency can be excluded if the saturation is more than 20% to 25%. A serum ferritin level of less than 20 ng per ml in a male patient or 10 ng per ml in a female patient is virtually diagnostic of iron deficiency.[5] In cases of chronic infection, inflammatory disorders or renal failure, a serum ferritin level of less than 50 ng per ml is very suggestive of iron deficiency. In the final step of heme synthesis, iron is inserted into protoporphyrin by the enzyme ferrochelatase to form heme. An increase in free erythrocyte protoporphyrin (FEP) content occurs when iron is not available (such as in patients with iron deficiency or anemia of chronic disease) or the ferrochelatase is dysfunctional (as in patients with lead poisoning). An FEP level (normal 15 to 85 $\mu$g per dl erythrocytes) is increased in patients with iron deficiency (FEP > 100 $\mu$g per dl erythrocytes), anemia of chronic disease and idiopathic refractory sideroblastic anemia, and usually substantially increased in those with lead poisoning ( > 250 $\mu$g per dl erythrocytes).[6] The FEP value is usually normal in patients with thalassemia[7] and may be used to differentiate thalassemia minor from the other causes of a microcytic anemia. A bone marrow aspirate for iron stain remains the "gold standard" for demonstrating iron deficiency anemia in difficult cases. To avoid a false-negative iron stain of the aspirate, one must obviously be certain that an adequate marrow particle has been obtained.[8] Except in cases of severe iron deficiency anemia (hemoglobin less than 6 to 8 grams per dl), an observable reticulocyte response to iron therapy is unlikely (more precise automated reticulocyte counts are being developed that may permit detection of small increments of response). An increase in the hemoglobin content of 1 gram per dl per week and full correction of the anemia can be expected in two months, however. The diagnosis of iron deficiency mandates a search for the source of blood loss.

TABLE 1.—*Causes of Microcytic Anemias*

| |
|---|
| Iron deficiency |
| Thalassemia minor |
| Anemia of chronic disease |
| Lead poisoning |
| Congenital sideroblastic anemia |
| $\beta$-Thalassemia intermedia and major |
| Hemoglobin H or E disease |

If thalassemia is suspected, a hemoglobin electrophoresis should be done and quantitative hemoglobin (Hb) $A_2$ and F levels measured. In most laboratories, a simple hemoglobin electrophoresis alone is not sufficiently accurate to measure the slight increases in Hb $A_2$ above the normal characteristic of $\beta$-thalassemia minor, but it will detect Hb H, E and other variant hemoglobin disorders that could present as microcytic anemia. With the decreased production of $\beta$-globin chains characteristic of $\beta$-thalassemia, the normal amounts of $\alpha$-chains combine with the $\delta$- and $\gamma$-globin to form increased amounts of Hb $A_2$ and F. Hb $A_2$ will be increased to 4% to 6% (normal < 2%). If $\beta$-thalassemia minor is complicated by concomitant iron deficiency, Hb $A_2$ levels may not be elevated. They will also not be increased in $\delta\beta$-thalassemia where both genes are deleted. Hb F levels will be increased in many patients with $\beta$-thalassemia minor and all patients with $\delta\beta$-thalassemia. If in a patient with hypochromic anemia, iron and Hb $A_2$ levels are normal, one is probably dealing with $\alpha$-thalassemia.

In $\alpha$-thalassemia, the excess $\beta$-chains have no $\alpha$ alternative to pair with and form $\beta_4$-tetramers (Hb H). For the first few months of life before the $\gamma$ to $\beta$ switch takes place, $\gamma_4$-tetramers (Hb Bart's) are formed in the $\alpha$-thalassemias. Newborns missing one $\alpha$-gene (silent carrier), two $\alpha$-genes (thalassemia minor), three $\alpha$-genes (Hb H disease) and four $\alpha$-genes (hydrops fetalis, stillborn) can be detected and separated by their clinical features, the MCV and by the amount of Hb Bart's present.[9] After the $\gamma$ to $\beta$ switch, the $\beta_4$-tetramers (Hb H), which are much less soluble than the $\gamma$-tetramers, can only be detected in patients missing three genes (Hb H disease). In summary, if the iron studies are normal and the

hemoglobin electrophoresis is normal, the cause of a microcytic anemia is presumed to be $\alpha$-thalassemia. Confirmation requires hemoglobin electrophoresis of newborn family members or restriction enzyme analysis of DNA.

The gene frequency for Hb E exceeds 10% in patients from some parts of Southeast Asia. With the recent influx of Asian immigrants to the United States, an increasing number of patients with Hb E are being seen. The substitution of lysine for glutamic acid at position 26 of the $\beta$-chain results in decreased production of $\beta$-chain due to abnormal messenger RNA splicing. Thus Hb E heterozygotes resemble patients who have $\beta$-thalassemia minor with microcytosis but without anemia.[10] Homozygotes still have minimal anemia or hemolysis but with more prominent target cells and more severe microcytosis. $\beta^E\beta^0$-thalassemia is one of the $\beta$-thalassemia intermedia syndromes. Hb E is easily detected on routine hemoglobin electrophoresis.

A hemoglobin level of less than 9 grams per dl in a patient with microcytic anemia and normal iron studies suggests Hb H disease, $\beta$-thalassemia major ($\beta^0\beta^0$) or $\beta$-thalassemia intermedia. All of these will be detected on the hemoglobin electrophoresis. Patients with $\beta$-thalassemia major (Cooley's anemia) have a severe anemia starting in infancy with massive hepatosplenomegaly, bone marrow expansion, abnormal facies and growth retardation unless maintained on a regular transfusion program. Their Hb F level is greatly increased, at times more than 90%. The $\beta$-thalassemia intermedia syndromes are characterized by a hemoglobin level of less than 9 grams per dl, but without the transfusion requirement. There are several causes including a genetic defect with some $\beta$-chain production ($\beta^+$ as in $\beta^0\beta^+$ or $\beta^+\beta^+$) or coexistent $\alpha$-thalassemia with $\alpha^0\beta^0$ (the reduction of $\alpha$-chain production limits the formation of unpaired $\alpha$-chains that participate in the membrane damage and intramedullary destruction of erythrocytes in the pathophysiology of the anemia). Hb H disease ($-\alpha/--$) also presents with a hemoglobin level of less than 9 grams per dl, but without the long-term transfusion requirement of patients with $\beta$-thalassemia major. Like $\beta$-thalassemia intermedia and major, there is pronounced anisocytosis and poikilocytosis in Hb H disease, with nucleated erythrocytes and usually splenomegaly, features not seen in thalassemia minor. Interestingly, Hb H disease can have exacerbations of the hemolytic process induced by oxidant drugs and infections just as in glucose-6-phosphate dehydrogenase (G6PD) deficiency and the unstable hemoglobins, which will be discussed below.

Long-standing anemia of chronic disease occasionally becomes mildly microcytic, but the MCV rarely falls below 78 cu microns. In these cases, the iron level and total iron-binding capacity will both be very low, and the serum ferritin level will not be less than 100 ng per ml (normal range, 12 to 300 ng per ml, mean 23 to 34 ng per ml for menstruating women and 92 to 94 ng per ml for men).[8] Iron deficiency and anemia of chronic disease may, of course, occur together, as in patients with inflammatory bowel disease and those with the rheumatic diseases treated with aspirin and nonsteroidal anti-inflammatory drugs. The iron saturation (iron/TIBC) may be quite low in these conditions even without iron deficiency. If, however, the saturation is greater than 30%, then iron deficiency is excluded. Because ferritin is an acute-phase reactant and serum levels tend to be elevated in inflammatory states, a serum ferritin value of less than 50 ng per ml in one of these disorders is very suggestive of iron deficiency.[5] When ferritin levels are borderline (50 ng per ml), one may need to obtain a bone marrow aspirate for iron stain to settle the question.

TABLE 2.—*Causes of a Mean Corpuscular Volume of Greater Than 100 Cubic Microns*

| |
|---|
| Megaloblastic anemia ($B_{12}$ or folate deficiency) |
| Alcoholism |
| Liver disease |
| Reticulocytosis |
| Chemotherapy |
| Myelodysplastic syndromes |
| Multiple myeloma |
| Spurious |
| Idiopathic |
| Sideroblastic anemia |
| Hypothyroidism |

Lead poisoning is a relatively uncommon cause of microcytic anemia, except in certain population groups, such as children living in an area where lead paint is prevalent or industrial workers with occupational exposure. Coarse basophilic stippling of erythrocytes is seen in lead poisoning, thalassemia and congenital erythrocyte pyrimidine 5′-nucleotidase deficiency. One needs to remember that ethylenediaminetetraacetic acid (EDTA) can abolish the stippling, so a blood smear examination should be made on a smear prepared from a finger-stick specimen of fresh blood from the tip of a needle. This practice applies not only to the search for basophilic stippling, but to evaluating peripheral blood smears in general because several artifacts can be induced by incubating blood in anticoagulated test tubes for even a few minutes to an hour. As discussed earlier, an increase in FEP levels occurs in lead poisoning and pyrimidine 5′-nucleotidase deficiency but not in thalassemia. Suspected lead poisoning should be confirmed by whole blood lead concentrations, increased urinary $\delta$-aminolevulinic acid and coproporphyrin levels or a 24-hour urinary lead excretion after a provocative injection of EDTA.

Sideroblastic anemia is sometimes listed as a cause of microcytic anemia because of the presence of two cell populations—one microcytic—but, in fact, the MCV is always normal or slightly macrocytic,[11] with the exception of the congenital sideroblastic anemias. Congenital sideroblastic anemias are X-linked recessive, so primarily only males are affected. Although congenital, the onset may be delayed until adulthood. They are distinguished from acquired sideroblastic anemia by the low MCV, a uniform rather than dimorphic population of microcytic cells peripherally and the absence of dysplastic changes in marrow. This rare disorder is suggested if a microcytic anemia is found with a very high iron saturation and serum ferritin level unless the patient had thalassemia and had received many transfusions or had been mistakenly treated with iron supplements.

## Macrocytic Anemias

Similar to the finding of microcytosis, the finding of an MCV of more than 100 cu microns is quite helpful because of its limited differential diagnosis (Table 2).[12] An MCV of more than 120 cu microns almost always indicates megaloblastic anemia, and, in fact, most of the time the other causes on the list will lead to an MCV between 100 and 110 cu microns. The first step is to carefully examine the peripheral smear. The finding of hypersegmented polymorphonuclear

TABLE 3.—*Causes of Falsely Low and Normal $B_{12}$ Levels*

| *Inaccurate $B_{12}$ Levels* | *Causes* |
|---|---|
| Falsely low | Folate deficiency |
| | Multiple myeloma |
| | Waldenstrom's macroglobulinemia |
| | Recent nuclear scan |
| | Third trimester of pregnancy |
| | Transcobalamin I deficiency |
| | Advanced age (see text) |
| Falsely normal | Increase in transcobalamin I and III levels |
| | Chronic myelogenous leukemia or polycythemia vera |
| | Severe liver disease |

TABLE 4.—*Limitations of Erythrocyte Folate Measurements*

| *Inaccurate Erythrocyte Folate Levels* | *Causes* |
|---|---|
| Falsely low | Vitamin $B_{12}$ deficiency |
| Falsely normal | Transfusion |
| | Early folate deficiency |

leukocytes in this setting means megaloblastic anemia—either vitamin $B_{12}$ or folate deficiency. Hypersegmentation is defined as a mean neutrophilic lobe count of greater than 3.2. Clinically, the finding of one 7-lobed neutrophil, two 6-lobed neutrophils or three 5-lobed neutrophils strongly suggests megaloblastic anemia. Other rare causes of hypersegmentation include congenital hypersegmentation and renal failure. Oval macrocytes on the peripheral smear are another sign of megaloblastosis; they are more sensitive but somewhat less specific than neutrophil hypersegmentation in predicting marrow megaloblastic changes.

In most cases, the finding of macrocytosis should prompt a determination of vitamin $B_{12}$ and folate levels. A low vitamin $B_{12}$ or folate level, however, in the absence of oval macrocytes or at least borderline hypersegmentation on a carefully examined peripheral smear should be regarded as possibly spurious, or not the primary cause of the macrocytic anemia. The old microbiologic determination of $B_{12}$ levels has been replaced with radioimmunoassays, and many of the methodologic problems that plagued the early radioimmunoassays have been eliminated. There remains, however, a large number of patients with a low vitamin $B_{12}$ level but normal bone marrow and a negative Schilling test. Some of these patients have subtle abnormalities of vitamin $B_{12}$ absorption due to preclinical pernicious anemia or impaired gastric function that can be elicited by tests wherein the vitamin $B_{12}$ is given bound to protein such as egg yolk.[13] Many of these patients have been found to have abnormal deoxyuridine suppression.[14] This can be tested only at research centers at this time and involves culturing bone marrow cells. Normally, deoxyuridine suppresses thymidine incorporation in cultured marrow cells. In the presence of vitamin $B_{12}$ or folate deficiency, reduced deoxyuridine suppression is corrected by the in vitro addition of the missing factor. This appears to be the best test for discriminating between vitamin $B_{12}$ and folate deficiency. Prospective studies are now under way to examine the clinical significance of a low $B_{12}$ level, abnormal deoxyuridine suppression, a negative Schilling test and no megaloblastic changes in the marrow. The causes of falsely low and falsely normal vitamin $B_{12}$ levels are given in Table 3.

Tests of serum folate levels have been replaced in many laboratories by those of erythrocyte folate levels because the amount of serum folate is a poor reflection of tissue folate stores. Particularly problematic was the rapid correction of serum folate after one meal in hospital while tissue stores of folate remained depleted. Erythrocyte folate levels are still subject to falsely low and falsely normal results, as seen in Table 4. One of the chief drawbacks of measuring the erythrocyte folate level is that in up to half of patients with pure vitamin $B_{12}$ deficiency, the erythrocyte folate level will be falsely low. Conversely, as many as half of patients with folate deficiency have a low serum $B_{12}$ level that corrects with folate repletion alone. While some patients may be truly depleted of both vitamins, in most cases this does not appear to be so. Thus, a clinician is often faced with a patient with a megaloblastic anemia and low $B_{12}$ and erythrocyte folate levels.

In a patient with severe megaloblastic anemia, the safest approach would be to determine the vitamin $B_{12}$ and folate levels and immediately replace both vitamin $B_{12}$ (100 $\mu$g given intramuscularly weekly) and folate (1 mg by mouth or parenterally, then 1 mg a day); a Schilling test should be done one to four weeks later. In milder cases, one can give a trial of vitamin $B_{12}$ alone (1 $\mu$g per day) and observe for a brisk reticulocyte response four to ten days later. Iron stores are usually increased in megaloblastic anemia; in the absence of abundant iron, the reticulocyte response may be blunted. One could theoretically do the same thing with a very low dose of folate, such as 50 $\mu$g orally, which would correct folate but not vitamin $B_{12}$ deficiency. (But remember that large doses of folate will correct the hematologic abnormalities of vitamin $B_{12}$ deficiency but still permit the neurologic damage to progress.) Another approach to separating the two deficiencies takes advantage of the fact that the conversion of methylmalonic acid to succinyl-CoA in propionic acid metabolism is vitamin $B_{12}$ but not folate-dependent. Vitamin $B_{12}$ deficiency, but not folate deficiency, results in increased levels of methylmalonic acid in the urine. Conversely, folate but not vitamin $B_{12}$ participates in the conversion of formiminoglutamic acid to glutamic acid in the histidine pathway. Although urinary excretion of formiminoglutamic acid is increased in patients with folate deficiency, it may also be increased in those with vitamin $B_{12}$ deficiency, and this lack of specificity limits its clinical usefulness. As discussed earlier, the deoxyuridine suppression test appears to be the most sensitive indicator of early megaloblastosis and can identify the specific deficiency involved, but at this time it is only available in research centers.

If there is any doubt as to the cause of a case of macrocytic anemia, a bone marrow aspirate and biopsy should be done. In classic megaloblastic anemia, one will see increased cellularity in the biopsy specimen. The aspirate will show erythroid hyperplasia, delayed nuclear maturation relative to the hemoglobinization of the cytoplasm seen best in the basophilic, polychromatophilic and orthochromatic erythroblasts, increased cytoplasm and a characteristic megaloblastic look to the chromatin of the nucleus ("tapioca pudding"). The characteristic myeloid forms are the giant metamyelocyte and band. The myelodysplastic syndromes may also show increased marrow cellularity with megaloblastic features, but one will generally also see dysplastic features like uninuclear megakaryocytes or megakaryocytes with multiple separated nuclei, increased myeloblasts, ringed sideroblasts or more impressive erythroblast multinuclearity and nuclear fragmentation than in megaloblastic anemia.

Continuous exposure to nitrous oxide (more than six hours) can also induce megaloblastic changes in the marrow and a positive deoxyuridine suppression test with normal serum vitamin $B_{12}$ levels, probably by interfering with the cobalt atom in vitamin $B_{12}$.[15] Interestingly, a diffuse polyneuropathy more sensory than motor and myelopathy affecting corticospinal tracts and posterior columns similar to subacute combined degeneration in vitamin $B_{12}$ deficiency may occur from occupational or recreational exposure to nitrous oxide.[16] A recent report by Schilling[17] suggests that nitrous oxide anesthesia may cause significant neurologic dysfunction in persons with unrecognized deficiency of vitamin $B_{12}$ or folate.

Once vitamin $B_{12}$ or folate deficiency is diagnosed, one must identify the cause. The causes of vitamin $B_{12}$ deficiency are reviewed in Table 5. Although anti-intrinsic factor antibody is found in only about 50% to 60% of patients with pernicious anemia, it is very specific for this disorder and therefore useful because it makes it unnecessary to do a Schilling test. Antiparietal cell antibodies are more sensitive but much less specific and therefore not helpful. Achlorhydria is also a nonspecific finding, occurring in causes of vitamin $B_{12}$ deficiency other than pernicious anemia and in some normal elderly patients. If one finds gastric acid, however, pernicious anemia is excluded. In summary, unless one can detect anti-intrinsic factor antibodies, the finding of a low vitamin $B_{12}$ level should be followed up with a Schilling test. If phase 1 is abnormal (radiolabeled vitamian $B_{12}$ alone) and phase 2 is normal (radiolabeled vitamin $B_{12}$ plus intrinsic factor) and the patient has not had a total gastrectomy, then the diagnosis is pernicious anemia. If phases 1 and 2 are abnormal, then there is small bowel disease, fish tapeworm or bacterial overgrowth. If bacterial overgrowth is suspected, then phase 2 can be repeated after two weeks of tetracycline therapy (the so-called phase 3 Schilling). On occasion, a patient with pancreatic insufficiency will fail to digest gastric R proteins that bind to the vitamin $B_{12}$, making it unavailable to intrinsic factor and giving a positive Schilling test.[18] If the Schilling test is negative but the vitamin $B_{12}$ level is low and the marrow megaloblastic, then one of the more sensitive Schilling tests can be done.[13] The double isotope Schilling test, in which phases 1 and 2 are done simultaneously using different isotopes to save time, is not recommended at present because of technical problems.[19] The addition of a plasma as well as urinary determination of radioactivity appears to be a useful refinement of the traditional test to avoid the errors of incomplete urine collection. If one is aware of the potential errors in the Schilling test,[12] it remains the gold standard for the diagnosis of pernicious anemia. Patients with a new diagnosis of pernicious anemia should have a thyroid-stimulating hormone level measured because of the high incidence of Hashimoto's thyroiditis and the often cryptic presentation of hypothyroidism.

TABLE 5.—*Causes of True Vitamin $B_{12}$ Deficiency*

| |
|---|
| Pernicious anemia |
| Gastrectomy or severe gastritis |
| Pancreatic insufficiency |
| Disease or resection of the terminal ileum |
| Bacterial overgrowth of small bowel |
| *Diphyllobothrium latum* |
| Transcobalamin II deficiency |
| Continuous administration of nitrous oxide |
| Strict vegetarianism |

TABLE 6.—*Causes of True Folate Deficiency*

| |
|---|
| Dietary deficiency, especially in association with alcoholism |
| Pregnancy |
| Chronic hemolytic anemia, such as sickle cell anemia |
| Chronic desquamative skin diseases, such as psoriasis |
| Renal failure with hemodialysis or peritoneal dialysis |
| Drugs |
| Phenytoin |
| Sulfamethoxazole-trimethoprim |
| Methotrexate |
| Alcohol |
| Oral contraceptives |
| Severe small bowel disease |
| Crohn's disease |
| Lymphoma or leukemia infiltration |
| Tropical and nontropical sprue |
| Scleroderma |
| Diabetes mellitus |
| Amyloidosis |

The follow-up evaluation of low folate but normal $B_{12}$ levels should include a review of the list of causes of low folate levels (Table 6). Unless an obvious dietary cause is found, one should evaluate small bowel function (such as with a D-xylose test, fecal fat or upper gastrointestinal tract x-ray films and small bowel follow-through).

Patients with the nonmegaloblastic macrocytic anemias almost always have an MCV of less than 120 cu microns and usually less than 110 cu microns. Alcohol ingestion (six beers or two to three drinks per day) is probably the commonest cause of mild macrocytosis.[20] Liver disease can also cause mild macrocytosis. Chemotherapy commonly induces a macrocytic anemia, often with some dysplastic peripheral blood and bone marrow features. Severe hypothyroidism may cause macrocytic anemia, but this is uncommon unless there is coexistent $B_{12}$ deficiency (Hashimoto's thyroiditis and pernicious anemia). The anemia of hypothyroidism may be normocytic or microcytic (if there is iron deficiency from heavy menstrual bleeding related to the hypothyroidism). Because the MCV of a reticulocyte is almost 160 cu microns, pronounced reticulocytosis will increase the MCV, but never to more than 120 cu microns. Furthermore, polychromasia should be obvious on a peripheral smear and easily confirmed with a reticulocyte count. Cold agglutinins and multiple myeloma can cause a falsely elevated MCV because the erythrocytes stick together and the electronic counter treats a clump as one cell. One should see agglutination on a peripheral smear in these cases, and the RDW will be increased. Spurious macrocytosis can be caused by hyperglycemia and hypernatremia because the erythrocytes are placed in isotonic medium before counting and swell.

Aplastic anemia and the myelodysplastic syndromes are commonly associated with mild macrocytosis. Features on the peripheral smear that suggest myelodysplasia include giant platelets or platelets with abnormal clumping of or decreased quantities of granules, hypogranular polymorphonuclear leukocytes or particularly bilobed neutrophils (pseudo-Pelger Huet cells). The bone marrow features of myelodysplasia were discussed earlier in the differential of megaloblastic marrow.[21] A bone marrow diagnosis is essential for accurately determining a prognosis with regard to the risk for transformation to acute leukemia.

### Normocytic Anemia With Reticulocytosis

There are three causes of normocytic anemia with an increased number of reticulocytes: bleeding, recent correction of a production defect and hemolysis. In the absence of obvious external or occult gastrointestinal blood loss, one should consider occult retroperitoneal, pelvic or deep muscle bleeding. Anemia with an increased reticulocyte count may occur following repletion of $B_{12}$ or folate (note that the neutrophil hypersegmentation will persist for 7 to 14 days)[22] but not usually with iron replacement. This may also occur with removal of a marrow suppressant like alcohol or with the treatment of infection. The third cause of a normocytic anemia with an increased reticulocyte count is hemolysis. Hemolysis is suggested by elevated bilirubin and lactic dehydrogenase (LDH) levels, a peripheral smear showing schistocytes or spherocytes, or dark urine. While an elevated LDH level is nonspecific, a normal LDH value is against ongoing hemolysis and an extremely high LDH favors it. The bilirubin is roughly proportional to the erythrocyte mass so that a bilirubin of 1.0 mg per dl with a hemoglobin of 10 grams per dl and an increased reticulocyte count is suggestive of hemolysis.[23]

If the number of reticulocytes is reported as a crude percentage, then it should be corrected for the degree of anemia by multiplying the observed reticulocyte count by the observed hematocrit concentration divided by 45 to achieve a more meaningful assessment of marrow production. Normally, reticulocytes are recognizable by a supravital stain in the peripheral blood for one day after they are released from the marrow. With increasing degrees of anemia, the reticulocytes are released earlier from the marrow and therefore are present longer in the peripheral blood. Thus at a hematocrit of 35%, the reticulocyte lifespan in the peripheral blood is 1.5 days; at a hematocrit of 25% it is 2 days, and at a hematocrit of 15% it is 2.5 days.[24] To accurately assess the daily reticulocyte production, a second correction should be made for this "shift" phenomenon. The above reticulocyte "index" or absolute reticulocyte percentage is divided by 2 for a moderate anemia (with a hematocrit of around 25%) and divided by 3 for a severe anemia (with a hematocrit of around 10%). In response to acute bleeding or hemolysis, a normal bone marrow should increase its daily production to 2% reticulocytes at a hematocrit of 35%, and to 3% with severe anemia (hematocrit of 10%).

In the further evaluation of suspected hemolysis, it is useful to determine whether erythrocytes are being destroyed intravascularly or extravascularly (in the spleen) because only a limited number (Table 7) of disorders causes intravascular hemolysis and because intravascular hemolysis may result in acute renal failure and disseminated intravascular coagulation (DIC). The intravascular lysis of even a few erythrocytes will turn the plasma red or brown. The hemoglobin is picked up by haptoglobin until the haptoglobin is saturated, at which time free hemoglobin is filtered at the glomerulus resulting in hemoglobinuria. The urine will be red or brown and dipstick-positive for blood, but without erythrocytes on microscopic examination. Although the urine in cases of myoglobinuria will appear the same, the plasma is clear because the smaller myoglobin molecule is so rapidly cleared. Some of the hemoglobin that is filtered by the glomerulus will be taken up by renal tubular epithelial cells that slough several days later, leading to a positive urine hemosiderin test. Increased LDH levels, reduced haptoglobin and increased indirect bilirubin

TABLE 7.—*Causes of Intravascular Hemolysis*

| |
|---|
| Glucose-6-phosphate dehydrogenase deficiency |
| Microangiopathic hemolytic anemia |
| ABO-incompatible blood transfusion |
| Cold antibody autoimmune hemolytic anemia (cold agglutinin disease) |
| Warm antibody autoimmune hemolytic anemia |
| Paroxysmal cold hemoglobinuria |
| Paroxysmal nocturnal hemoglobinuria |
| Clostridial sepsis |
| Delayed hemolytic transfusion reaction |

TABLE 8.—*Causes of Microangiopathic Hemolytic Anemia*

| |
|---|
| Disseminated intravascular coagulation |
| Thrombotic thrombocytopenic purpura |
| Malignant hypertension |
| Eclampsia |
| Vaculitis |
| Metastatic cancer |
| Extreme turbulence due to major abnormalities within the heart or great vessels |
| Sepsis |

occur with both intravascular and extravascular hemolysis. Therefore, the first steps in evaluating suspected hemolysis are to visually inspect the plasma in a spun specimen, to inspect the urine and examine it under the microscope for erythrocytes and to test it with a dipstick for blood.

If there is evidence of intravascular hemolysis, the next steps are to examine the smear for evidence of microangiopathic changes and to order a Coombs' test and a Heinz body preparation. At times, the microangiopathic changes may be relatively subtle; if there is one or two schistocytes, fragmented cells or helmet cells per high-power field, then one needs to consider the differential diagnosis of the microangiopathic syndromes (Table 8). If the platelet count is low or falling, one needs to strongly consider DIC, thrombotic thrombocytopenic purpura or the hemolytic uremic syndrome. Prolongation of the thrombin time, prothrombin time and partial thromboplastin time, reduction of the fibrinogen level, elevation of the fibrin-split products and a positive fibrin monomer are seen in patients with DIC, but the results of these tests are relatively normal in thrombotic thrombocytopenic purpura and the hemolytic uremic syndrome. Fever, a fluctuating neurologic status and only mildly abnormal blood urea nitrogen and creatinine levels in an adult suggest thrombotic thrombocytopenic purpura. Acute oliguric renal failure with a relatively normal neurologic status in a child suggests the hemolytic uremic syndrome.

While warm autoimmune hemolytic anemia only rarely causes intravascular hemolysis, it is easily discovered by a positive direct Coombs' test, reflecting immunoglobulin (Ig) G or C3 on the surface of the erythrocytes. If one finds only C3 on the surface of the erythrocytes, then the diagnosis is most likely cold agglutinin disease. The IgM is bound to the erythrocytes in cooler areas of the body and fixes C3, but upon rewarming, the IgM diffuses off, leaving C3 alone when the Coombs' test is done.

If there is evidence of intravascular hemolysis but the peripheral smear is normal and the Coombs' test is negative, one should suspect G6PD deficiency. A Heinz body preparation may show the oxidized and precipitated hemoglobin

during and briefly after an episode of acute G6PD hemolysis. In the African or B-type of G6PD deficiency, which occurs in 12% of American blacks, the enzyme is unstable and has a shorter than normal half-life so that the older erythrocytes have the lowest levels and are susceptible to hemolysis with infection, acidosis or oxidant drugs. In these patients, the hemoglobin level will drop suddenly from normal to about 8 to 9 grams per dl and then stop or even rise again. Because all of the older cells have been destroyed, one will have to wait six to eight weeks and then assay the G6PD. In the Mediterranean and Chinese varieties of G6PD deficiency, the defect is more profound and affects all cells so that patients' hemoglobins will not stabilize at 8 to 9 grams per dl, but may fall to extremely low levels if the oxidant stress continues. In these patients, the G6PD assay is often diagnostic even after an episode of hemolysis.

Two other causes of intravascular hemolysis are paroxysmal cold hemoglobinuria and paroxysmal nocturnal hemoglobinuria. Paroxysmal cold hemoglobinuria is due to a cold-reactive IgG that on rewarming activates the full complement sequence with brisk intravascular hemolysis. The cold IgG—the Donath-Landsteiner antibody—used to be seen in patients with congenital and tertiary syphilis, but today is usually postviral or idiopathic. One needs to specifically do a Donath-Landsteiner test because the Coombs' test may be negative. In paroxysmal nocturnal hemoglobinuria, the hemoglobin level is usually low, but may be normal. The leukocyte and platelet counts are usually reduced. Paroxysmal nocturnal hemoglobinuria should always be considered in the differential diagnosis of pancytopenia, particularly with increased reticulocytes. The leukocyte alkaline phosphatase score is low in cases of this disorder. The two best screening tests are the urine hemosiderin and the sucrose hemolysis tests. The urine hemosiderin test is almost always positive. The sucrose hemolysis may on occasion be normal, particularly after an episode of hemolysis has reduced the number of abnormal cells. A positive sucrose hemolysis test should be confirmed with the complete Ham's acid hemolysis test.

In the absence of hemoglobinemia or hemoglobinuria, the hemolysis may still have been intravascular and missed, but is probably extravascular. It is useful to know what a previous complete blood count was because almost all new cases of hemolytic anemia in adults are autoimmune hemolytic anemia, G6PD deficiency or, less commonly, microangiopathic hemolytic anemia. Evaluation begins by examining the smear. The significance of microangiopathic changes has been discussed. True spherocytes (small, darkly pigmented and without central pallor) suggest autoimmune hemolytic anemia or hereditary spherocytosis; spherocytes may also be seen with severe burns. Therefore, in a new case of hemolytic anemia, spherocytes are very suggestive of autoimmune hemolytic anemia. A Coombs' test should be done even if the erythrocytes look normal. If spherocytes are seen and the Coombs' test is negative, an osmotic fragility test (or, preferably, ektacytometry) should be done.[25] Ektacytometry is a new technique, not widely available, that appears to be more sensitive than simple osmotic fragility testing for hereditary spherocytosis and other defects of the erythrocyte cytoskeleton. The erythrocytes are suspended in an osmotic medium that can be varied from hypotonic to hypertonic, simultaneously subjected to a shear stress and their instantaneous deformability measured by laser diffraction. If the Coombs' and osmotic fragility tests are negative, a "micro" or "super" Coombs' test should be done. A standard Coombs' test will detect more than 500 molecules of IgG per erythrocyte. The micro-Coombs' test will detect between 50 and 500 molecules per cell, which occurs in 2% to 5% of cases of autoimmune hemolytic anemia. The new onset of hemolytic anemia with a normal smear and a negative Coombs' test, especially in the proper population group, is very suggestive of G6PD deficiency. As noted above, 12% of black men and boys in this country are affected by this X-linked recessive disorder; 1% of black women and girls are homozygous and affected and 25% of black women and girls are carriers, of whom a fourth are subject to hemolysis by lyonization with excessive inactivation of the normal X chromosome.

If the answer is not forthcoming from the above evaluation, it is helpful to retreat to a more formal consideration of the causes of hemolysis. Traditionally, these are divided into defects within erythrocytes, in the membrane of erythrocytes and outside of erythrocytes. Within erythrocytes, one may have defects in either the hemoglobin or the enzymes. Sickle cell anemia is obvious from a smear. The thalassemias are microcytic and have been discussed above. It is worthwhile to recall that Hb H disease ($--/-\alpha$) can have drug- and infection-induced exacerbations of hemolysis like G6PD deficiency. The unstable hemoglobins are uncommon and usually present as a chronic nonspherocytic hemolytic anemia from childhood. Some, however, may be mild, but patients can have oxidant-induced hemolysis and therefore the disorder appears as an acquired hemolytic anemia. Unstable hemoglobins are detected with incubation with brilliant cresyl blue, resulting in the formation of Heinz bodies.[26] This will also occur in patients with Hb H disease and G6PD deficiency. Other tests include hemoglobin electrophoresis and incubation with 17% isopropanol at 37°C or heating to 50°C to look for instability and precipitation.[17] Of the enzyme deficiencies, G6PD is by far the most common. Pyruvate kinase is the next most common enzyme deficiency and accounts for 95% of the glycolytic pathway deficiencies. Glucose phosphate isomerase accounts for about 4% and the rest are extremely rare.[27] Pyrimidine 5′-nucleotidase deficiency causes basophilic stippling and a microcytic anemia.

Of the membrane defects, hereditary spherocytosis, elliptocytosis and stomatocytosis should be obvious from the peripheral smear. Major advances have occurred in our understanding of the molecular basis of these disorders, all of which appear to involve defects in the erythrocyte cytoskeleton. Although these disorders are congenital, it is not uncommon for them to be detected for the first time in adulthood. Any insult that causes the marrow to stop producing may cause an aplastic crisis with a rapid fall in the hematocrit. In addition, these patients have gallstones at an early age and are at some increased risk of splenic rupture from their splenomegaly. All three disorders will show increased autohemolysis when defibrinated sterile blood is incubated for 48 hours, although this test is rarely done today. In addition, the results of osmotic fragility testing and ektacytometry will be abnormal.

Defects outside the erythrocyte besides autoimmune hemolytic anemia and microangiopathic processes include sepsis (especially clostridial sepsis), severe hypophosphatemia ($< 1$ mg per dl) and Wilson's disease.

## Normocytic Anemia Without Reticulocytosis

The differential diagnosis of anemia with an erythrocyte MCV of between 80 and 100 cu microns without an increase

TABLE 9.—*Causes of Normocytic Anemia Without Increased Reticulocytes*

| |
|---|
| Anemia of chronic disease |
| Early iron deficiency |
| Megaloblastic anemia with $\alpha$-thalassemia or iron deficiency |
| Hypoendocrine states |
| Renal failure |
| Acquired immunodeficiency syndrome |
| Aplastic anemia |
| Pure red cell aplasia |
| Anorexia nervosa |
| Bone marrow infiltration |
| Leukemia |
| Lymphoma |
| Cancer |
| Granulomatous diseases |
| Myeloproliferative disorder |

in reticulocytes is shown in Table 9. Within the past few years, it has been recognized that megaloblastic anemia may occasionally be normocytic,[28] particularly in populations with an increased prevalence of $\alpha$-thalassemia or iron deficiency. One would still expect to find hypersegmentation of polymorphonuclear leukocytes and oval macrocytosis, and the RDW would be increased. Probably the most common causes of a decreased-production normocytic anemia are early iron deficiency and the anemia of chronic disease. While the MCV generally does not fall below 80 cu microns in iron deficiency until the hemoglobin level is less than 10 grams per dl, the RDW will increase very early in the development of iron deficiency. Measurement of the serum iron level, TIBC and the serum ferritin level will resolve this. The pathophysiology of the anemia of chronic disease that involves decreased release of iron from reticuloendothelial stores, shortened red cell survival and decreased response to erythropoietin occurs within hours of the onset of infection or inflammation, and one may reasonably expect the hematocrit of a sick patient in hospital having daily blood tests to fall by 1% per day. One needs to assess the blood urea nitrogen and creatinine levels because renal failure is a common cause of decreased-production anemia. Hypoendocrine states and, in particular, hypothyroidism also result in a hypoproductive anemia. Due to its often subtle presentation, particularly in the elderly, one should have a low threshold of suspicion for checking the thyroid-stimulating hormone levels. Hypersplenism may cause a normocytic anemia with or without mild to moderate reticulocytosis. Generally one will also have moderate thrombocytopenia and leukopenia. The spleen need not be palpably enlarged. The bone marrow is generally hyperplastic and nonspecific unless also involved by the process causing the hypersplenism.

Multiple myeloma may present as a normocytic or macrocytic anemia and may be screened for with a serum protein electrophoresis and urinary immunoelectrophoresis. Myelofibrosis presents a leukoerythroblastic smear with nucleated and teardrop-shaped erythrocytes, an increase in the leukocyte count or the presence of early myeloid forms and giant platelets. Similar changes, but usually of a lesser degree, may be found with metastatic cancer, leukemia, lymphoma or granulomatous disease involving the marrow. There are, however, a number of benign disorders that can mimic these features[29] so that a bone marrow aspirate, biopsy and specimens for culture need to be obtained. Similar to the leukoerythroblastic disorders, the diagnosis of pure red cell aplasia or aplastic anemia requires examining the bone marrow. Thus, unless one finds evidence of iron deficiency, renal failure or hypothyroidism, a bone marrow examination is necessary.

Many patients with the acquired immunodeficiency syndrome (AIDS) or AIDS-related complex (ARC) will have anemia or pancytopenia in the course of their illness. The peripheral smear is usually unrevealing. The findings of a bone marrow examination in patients with AIDS or ARC are usually nonspecific with increased cellularity, an increase in plasma cells and eosinophils and often some fibrosis. Mycobacterial infections in AIDS patients may occur without granulomas, emphasizing the importance of specific stains for acid-fast bacilli and culturing the marrow for bacteria, fungus and typical and atypical mycobacteria.

## Conclusion

The clinical evaluation of anemia begins with the history, physical examination, complete blood count including RDW, reticulocyte count and examination of the peripheral smear. With these data, one generates a limited differential diagnosis, with one or two statistically likely possibilities and a few to several uncommon possibilities. During the past decade, the procedures used for confirming suspected vitamin $B_{12}$ and folate deficiencies have changed, and one needs to be aware of the causes of falsely low and falsely negative studies. The procedures for delineating the causes of microcytic and normocytic anemias with or without reticulocytosis have been refined but remain fundamentally unchanged. A systematic but focused approach to the laboratory evaluation of anemia results in expedient and precise diagnosing and avoids unnecessary testing.

### REFERENCES


1. Gottfried EL: Erythrocyte indexes with the electronic counter (Letter). N Engl J Med 1979; 300:1277

2. England JM: Future needs and expected trends in peripheral blood cell analysis: Erythrocyte histograms. Blood Cells 1985; 11:61-76

3. Bessman JD, Gilmer PR Jr, Gardner FH: Improved classification of anemias by MCV and RDW. Am J Clin Pathol 1983; 80:322-326

4. Bessman JD, Feinstein DI: Quantitative anisocytosis as a discriminant between iron deficiency and thalassemia minor. Blood 1979; 53:288-293

5. Halliday JW, Powell LW: Serum ferritin and isoferritins in clinical medicine. Prog Hematol 1979; 11:229-266 (174 ref)

6. Center for Disease Control Committee (Needleman HL, Chair): Preventing lead poisoning in young children. J Pediatr 1978; 93:709-720

7. Koenig HM, Lightsey AL, Schanberger JE: The measurement of free erythrocyte protoporphyrin as a means of differentiating $\alpha$-thalassemia trait from iron deficiency anemia. J Pediatr 1975; 86:539-541

8. Cook JD: Clinical evaluation of iron deficiency. Semin Hematol 1982; 19:6-18

9. Pearson HA: Disorders of hemoglobin synthesis and metabolism, *In* Oski FA, Naiman JL (Eds): Hematologic Problems in the Newborn, 3rd Ed. Philadelphia, WB Saunders, 1982, pp 245-282

10. Fairbanks VF, Gilchrist GS, Brimhall B, et al: Hemoglobin E trait reexamined: A cause of microcytosis and erythrocytosis. Blood 1979; 53:109-115

11. Beris P, Graf J, Miescher PA: Primary acquired sideroblastic and primary acquired refractory anemia. Semin Hematol 1983; 20:101-113

12. Carmel R: The laboratory diagnosis of megaloblastic anemias. West J Med 1978; 128:294-304

13. Dawson DW, Sawers AH, Sharma RK: Malabsorption of protein-bound vitamin $B_{12}$. Br Med J 1984; 288:675-678

14. Carmel R, Karnaze DS: The deoxyuridine suppression test identifies subtle cobalamin deficiency in patients without typical megaloblastic anemia. JAMA 1985; 253:1284-1287

15. Amess JAL, Burman JF, Rees GM, et al: Megaloblastic haemopoiesis in patients receiving nitrous oxide. Lancet 1978; 2:339-342

16. Layzer RB: Myeloneuropathy after prolonged exposure to nitrous oxide. Lancet 1978; 2:1227-1230

17. Schilling RF: Is nitrous oxide a dangerous anesthetic for vitamin $B_{12}$-deficient subjects? JAMA 1986; 255:1605-1606

18. Marcoullis G, Parmentier Y, Nicolas J, et al: Cobalamin malabsorption due

to nondegradation of R proteins in the human intestine. J Clin Invest 1980; 66:430-440

19. Lindenbaum J: Status of laboratory testing in the diagnosis of megaloblastic anemia. Blood 1983; 61:624-627

20. Lindenbaum J: Folate and vitamin $B_{12}$ deficiencies in alcoholism. Semin Hematol 1980; 17:119-129

21. Bennett JM, Catovsky D, Daniel MT, et al: Proposals for the classification of the myelodysplastic syndromes. Br J Haematol 1982; 51:189-199

22. Nath BJ, Lindenbaum J: Persistence of neutrophil hypersegmentation during recovery from megaloblastic granulopoiesis. Ann Intern Med 1979; 90:757-760

23. Berlin NI, Berk PD: Quantitative aspects of bilirubin metabolism for hematologists. Blood 1981; 57:983-999

24. Hillman RS, Finch CA: The misused reticulocyte. Br J Haematol 1969; 17:313-315

25. Clark MR, Mohandas N, Shohet SB: Osmotic gradient ektacytometry: Comprehensive characterization of red cell volume and surface maintenance. Blood 1983; 61:899-910

26. Carrell RW, Kay R: A simple method for the detection of unstable haemoglobins. Br J Haematol 1972; 23:615-619

27. Beutler E: Red cell enzyme defects as nondiseases and as diseases. Blood 1979; 54:1-7

28. Green R, Kuhl W, Jacobson R, et al: Masking of macrocytosis by alpha-thalassemia in blacks with pernicious anemia. N Engl J Med 1982; 307:1322-1325

29. Weick JK, Hagedorn AB, Linman JW: Leukoerythroblastosis: Diagnostic and prognostic significance. Mayo Clinic Proc 1974; 49:110-113

# Software Review

*The Western Journal of Medicine does not review all books or other material sent by publishers, although information about new books received is printed elsewhere in the journal as space permits. Prices quoted are those given by the publishers.*

## Hypertensive Emergencies

Edward P. Hoffer, MD, Lecturer in Medicine, Harvard Medical School, Associate Professor of Medicine, University of Massachusetts Medical School, and Senior Scientist, Laboratory of Computer Science, Massachusetts General Hospital, and G. Octo Barnett, MD, Professor of Medicine, Harvard Medical School, Physician, Massachusetts General Hospital, and Director, Laboratory of Computer Science, Massachusetts General Hospital, Boston. IBM-PC, PC/XT, PC/AT, or PCjr with 80-column display: minimum 128K memory, 1 double-sided disk drive, PC-DOS or MS-DOS 2.0 or higher; Apple II, all models: minimum 64K memory, 2 disk drives. Williams & Wilkins, 428 E Preston Street, Baltimore, MD 21202, 1985, $85.

*Review of Software*

In the past two years, a number of patient simulation programs have been written to run on microcomputers. Examples include programs by CME, Inc., associated with the University of Washington, the Scientific American Discotests, and the Williams and Wilkins RxDx series. This last series of ten or so programs deal primarily with cardiology issues. They have been authored by a group of physicians from the Massachusetts General Hospital. A recent addition to this series is "Hypertension Emergencies," authored by Edward Hoffer and Octo Barnett, both of the Laboratory of Computer Science at Massachusetts General Hospital.

The program comes on one disk, with a small booklet about using the program and a form to reply for CME credit (five hours). At $85, the price is a little steep when considered either as a computer program or home-based CME program. The program "boots" easily and is primarily menu based. One gets a choice of 18 patient simulations. Each simulation gives a brief history and physical, and then one primarily decides on pharmacological management.

The simulations are relatively short (five to ten screens), so that one doesn't get bored or engrossed in minutia. The directions are clear, and the program ran flawlessly. For a right answer chosen, the program gives a good pat on the back; if a wrong answer was chosen, there are additional loops that one goes through with screens of information and further questions. The screen fills in a jerky fashion from bottom to top, however, much like a piece of paper out of a printer, so that one has to wait for the screen to fill and stop moving before reading. The program was copyrighted in 1985, so that some of the information on the more newly released drugs is out of date.

My major criticism has to do with the direction and content of the program. Of the 18 cases, 17 dealt almost exclusively with drug management. The program sticks religiously to the stepped care approach. The program was a little more aggressive in recommending pharmacological treatment than I am (for instance recommending increased drug therapy in a middle-aged man with a blood pressure of 130/90). The patient education recommendations primarily emphasized getting the patients to take their medication each day. Only one of the simulations stressed low salt diet and exercise (but did give some good references). Many of the simulations seemed very repetitive, with a disproportionate number being black men who had very significant elevations of blood pressure that responded to diuretics and beta-blockers. Behavioral approaches and other nonpharmacologic treatments were rarely mentioned.

In conclusion, I think this program should be relabeled the "Pharmacologic Management of Hypertension." For most practicing physicians, I don't think it significantly adds to one's knowledge, unless one is not familiar with the stepped care approach and a couple of second line agents. The program might be more appropriate for medical students who are beginning to learn about decision making and drug therapy of hypertension. Overall, this is a straightforward but somewhat simple application of computer-based patient simulation. Its usefulness is limited.

JONATHAN E. RODNICK, MD
*University of California, San Francisco, School of Medicine*

Medical Progress

# Clinical Evaluation and Management of Transient Ischemic Attacks

JOHN F. ROTHROCK, MD, *San Diego*

*Transient ischemic attack (TIA) is a common but poorly understood disorder. Although it rightfully has been classified as a major risk factor for stroke, the majority of patients with TIAs do not suffer subsequent stroke, and it is unclear whether aggressive evaluation and treatment of TIA will significantly lower stroke risk. To effectively treat this disorder, the implications of transient cerebral ischemia and the basic pathophysiologic process underlying this condition must be understood, as well as the myriad of specific clinical causes that must be considered in any patient. Any less sophisticated approach will only propagate the confusion that already exists and lead to the use of therapies that may be useless or even harmful.*

(Rothrock JF: Clinical evaluation and management of transient ischemic attacks. West J Med 1987 Apr; 146:452-460)

If stroke is the sudden onset of a neurologic deficit caused by alteration in blood flow to a portion of the brain, then, by convention, transient ischemic attack (TIA) implies that the signs and symptoms generated by this process are not clinically detectable by 24 hours. TIA precedes a significant percentage of the roughly 500,000 new cases of stroke that occur annually in the United States, and many other patients will have TIAs without associated stroke. Despite its prevalence, what constitutes optimal clinical management of TIA remains highly controversial. The role of TIA as a major risk factor for stroke has been well established, but aggressive treatment of a patient with this condition has had little effect on reducing stroke incidence. Explanations for this past failure must be sought before a rational treatment plan can be assembled.

## TIA—Prognostic Implications

That TIA imparts an increased risk of stroke is accepted, but the magnitude of risk varies widely among published series. The true natural history of TIA is difficult to establish; most patients with TIA now receive some type of therapy—medical or surgical—and such treatment may well alter the outcome. Early studies involving untreated TIA patients are not particularly helpful, as reported incidences of subsequent stroke range from as low as 2% to as high as 50%.[1-9] More recent studies including treated patients have produced similarly conflicting results. In one widely quoted series, 24% of patients with carotid or vertebrobasilar TIAs suffered subsequent stroke by two years, and almost half of these occurred within the first month after TIA.[10] Toole and co-workers likewise found TIA an ominous prognosticator, with a combined stroke and death incidence of 63% over a mean follow-up of 5.5 years.[11] In a later study by Muuronen and Kaste, however, only 4.4% of TIA patients went on to experience stroke over a mean follow-up of 7.8 years.[12] Such widely divergent results call for closer scrutiny.

Of any study purporting to examine the prognosis of TIA, several key questions must be asked:

- *What are the demographic features of the study population?* Age, for example, will have a definite impact on stroke incidence, and other factors, including race and sex, may also influence outcome.
- *How rigorous are the study's diagnostic criteria?* For example, some investigators have included episodes of isolated true vertigo, a rather nonspecific symptom, in the patient group with vertebrobasilar TIA, perhaps helping to account for the low incidence of stroke after vertebrobasilar TIA reported in early series.[4,5,8,9] In addition, classification of TIA by subtype and angiographic correlation has not been attempted in most studies, and it is likely that the prognosis varies according to the subtype and associated anatomic cerebrovascular disease.
- *What effect has treatment had on the subject population?* For example, it seems unreasonable to lump patients undergoing endarterectomy with those never even receiving an angiogram, particularly if strokes occurring as a perioperative complication are regarded as part of the "natural history" of TIA.
- *How truly prospective is the study?* It appears that the period of highest risk for stroke lies within the first month after TIA, and perhaps even earlier (J.F. Rothrock, MD, and J. Corey-Bloom, MD, unpublished data, May 1986).[10] If a prognosis study includes patients who are presenting weeks after their TIAs—that is, already past the "high risk" period—results may be skewed towards a favorable outcome. Conversely, if patients are included who are in fact presenting with ischemic stroke, retrospectively examining the period just before stroke for evidence of an antecedent TIA will skew results towards a poorer outcome; most patients suffering stroke will seek medical attention, but patients experiencing TIAs only may disregard those symptoms and consequently exclude themselves from study.

Applying these criteria, review of the larger and more objective studies of the prognosis of TIA suggests a stroke

From the Division of Neurology, Department of Neurosciences, University of California, San Diego, Medical Center. Dr Rothrock is Director, UCSD Stroke Program. Reprint requests to John F. Rothrock, MD, Division of Neurology, Department of Neurosciences, UCSD Medical Center, 225 Dickinson St, San Diego, CA 92103.

ABBREVIATIONS USED IN TEXT

CNIT = carotid noninvasive testing
CT = computed tomography
TIA = transient ischemic attack

incidence of 4% to 10% within the year following the attack, with the highest risk period falling in the first month. All studies also cite an increased mortality risk, chiefly of cardiac origin. Given that not all TIAs lead to stroke, it is obviously crucial that we learn to determine which TIAs are especially ominous. Reflecting on the prognostic ambiguity of these attacks, Duncan and associates semifacetiously recommended we attempt to divide TIAs into TATWOD—"transient attacks that warn of disaster"—and BS—"brain spells" of uncertain cause and no prognostic significance.[13] An even more rigorous categorization would split TATWOD into "implicit" and "explicit" TIAs. Implicit TIAs, unlike "brain spells," are not completely benign but rather indicate underlying systemic atherosclerosis and thus imply an increased risk of stroke, coronary artery disease and other atherosclerotic complications relative to the general population. The stroke risk, however, is not dramatically increased and is not directly linked to the TIA, anatomically or temporally. Explicit TIAs, on the other hand, indicate a high risk of subsequent stroke that is directly linked to the TIA, occurring in that same vascular distribution and within a relatively short time. Little has emerged thus far to help us determine which TIAs have a more or less benign prognosis. Some investigators have reported a more favorable prognosis for TIA patients with normal angiograms,[14-17] but others have disputed this.[18,19] Although angiograms in patients with TIAs lasting an hour or more are frequently normal,[20,21] these long-duration attacks may indicate a higher risk of subsequent stroke.[13] Hemiplegic TIAs may be particularly ominous.[13] Attacks of transient monocular blindness (amaurosis fugax) have been reported to infrequently lead to hemispheric stroke,[22-24] but this has recently been questioned.[25] It is hoped that information enabling us to better differentiate between "brain spells" and implicit and explicit TIAs will be forthcoming.

## TIA Subtypes

The first step in evaluating a patient with presumed cerebral ischemic attacks involves excluding other possible causes for the clinical presentation. Table 1 lists conditions that may mimic TIA.

Once it has been determined that a patient has likely experienced a TIA, the natural inclination is to quickly initiate treatment. The complexities of TIA, however, defy casual diagnosis and frustrate those who seek a universally beneficial treatment plan. Many different processes may generate focal cerebral ischemia, and the specific process involved in each individual patient must be determined before treatment options are to be considered. Much of our failure to show real benefit from various treatments for TIA and stroke has resulted from the tendency to "lump together," to regard TIA and stroke as diagnoses per se and not as syndromes with diverse causes. Meticulous diagnostic categorization is often no simple task, but failure to adopt this approach will too often lead to the use of therapies that may be unnecessary and even harmful.

Focal cerebral ischemia may be produced by one of three basic mechanisms: (1) intrinsic obstruction of a large extracranial or intracranial vessel, with consequent reduced blood flow in the portion of the cerebrovascular tree supplied by that vessel, (2) intrinsic obstruction within small intracerebral branch vessels and (3) secondary embolic obstruction of a large, medium-sized or small intracranial vessel. Along with intracerebral and subarachnoid hemorrhage, these comprise the major subtypes of stroke (Table 2).

TIA is not commonly associated with primary hemorrhagic stroke, and the major task for a clinician lies in distinguishing between large-vessel obstruction, small-vessel obstruction and embolism as causes of TIA. The process of diagnosis does not end here, however, as even within each subtype many different causes coexist. For example, in the elderly population, TIAs induced by intrinsic large-vessel obstruction are usually a result of atherothrombosis, but in patients 45 years of age or younger, we have found arterial dissection, migraine and sympathomimetic drug use to be the

TABLE 1.—*Conditions That Can Mimic Transient Ischemic Attack*

| |
|---|
| Focal seizure activity |
| Migraine (?"spreading depression") |
| Compressive mononeuropathies (carpal tunnel syndrome, ulnar elbow compression and so forth) |
| Adams-Stokes syndrome |
| Brain tumor, with associated transient neurologic symptoms |
| Subdural hematoma |
| Demyelinating disease |
| Hypoglycemia, hyperglycemia |
| Primary ocular disease—glaucoma, vitreal hemorrhage, floaters and the like |
| Functional disorders—conversion hysteria, malingering, hyperventilation |

TABLE 2.—*Subtypes of Stroke*

| |
|---|
| Large vessel stenotic or occlusive |
| Small vessel stenotic or occlusive |
| Embolic |
| Intracerebral hemorrhage |
| Subarachnoid hemorrhage |

TABLE 3.—*Causes of Transient Ischemic Attack*

| |
|---|
| Large artery atherothrombosis with distal flow reduction |
| Small-vessel arteriosclerosis ("lacunar TIAs") |
| Cardiogenic emboli |
| Arterial-to-arterial emboli |
| Migraine (? vasospasm) |
| Arterial dissection |
| Vasculitis |
| Sympathomimetic drug use (? vasospasm versus vasculitis) |
| "Sludging"—polycythemia, sickle cell anemia, thrombocythemia and the like |
| Hypercoaguable states—puerperium, oral contraceptive use, "sticky platelet syndrome" and the like |
| Meningitis |
| Cortical vein thrombosis—dehydration, puerperium, infections, neoplasms and the like |
| Fibromuscular dysplasia |
| Moyamoya syndrome |
| Takayasu's arteritis |

TABLE 4.—*Ischemic Stroke Subtypes and Incidence of Antecedent Transient Ischemic Attack (TIA)*

| Stroke subtype | Antecedent TIA: Harvard Stroke Registry,* Percent | Antecedent TIA: UCSD Stroke Data Bank,† Percent |
|---|---|---|
| Large-vessel stenotic or occlusive (atherothrombotic) | 50 | 25 |
| Lacunar | 23 | 14 |
| Embolic | 11 (all sources) | 11 (cardiac only) |
| Unknown cause | .. | 10 |

*From Mohr.[26]
†From J.F. Rothrock, MD, and J. Corey-Bloom, MD, unpublished data

more common specific causes (J.F. Rothrock, MD, P.D. Lyden, MD, unpublished data, July 1986). Table 3 lists the major causes of ischemic TIA.

*Carotid Thrombosis*

Which TIAs indicate that a patient is at heightened risk for major stroke in that same vascular distribution? Of these, which may respond to therapeutic intervention? Of the ischemic stroke subtypes, large-vessel stenotic or occlusive stroke is most commonly heralded by TIA (Table 4). The grave disability often conveyed by this type of stroke and its possible amelioration by surgical or medical treatment have fueled a search for clinical features that might distinguish the associated TIAs from others of more benign origin. As noted previously, TIAs that last an hour or more may correlate with the absence of significant carotid stenosis on angiography,[20,21] and others have reported that TIAs of a short duration correlate well with carotid stenosis or occlusion.[27,28] A recent study, however, failed to show any correlation between attack duration and the presence or absence of anatomically significant carotid disease.[29] Multiple symptomatically stereotyped attacks have long been felt to indicate probable carotid stenosis, but this, too, has been recently questioned.[29] TIAs characterized by transient monocular blindness have correlated fairly well with ipsilateral carotid stenosis in most studies,[30-32] especially when associated with independently occurring "hemispheric" TIAs.[20] We have found that multiple attacks involving amaurosis fugax or "cortical" symptoms—dysphasia, hemianopsia, denial and the like—usually indicate significant carotid disease,[33,34] and we advocate emergency angiography for most patients with this clinical presentation.[33,34]

*Lacunar TIAs*

Lacunar infarction results from reduced blood flow to deep areas of brain supplied by small penetrating branches of the anterior, middle and posterior cerebral arteries, usually a result of lipohyalinotic obstruction within the small vessels themselves, often in association with chronic hypertension.[35,36] Lacunar stroke is often preceded by TIA,[26,36,37] and ischemia resulting from intrinsic small-vessel obstruction may cause transient neurologic signs and symptoms without leading to clinically overt stroke.[20,38,39]

It is obviously important not to confuse lacunar TIAs with those resulting from preocclusive large-vessel stenosis. Failure to recognize and treat the latter condition may lead to major stroke or death; conversely, mistaking lacunar TIAs for those generated by carotid thrombosis may result in exposing a patient to an unnecessary surgical risk. Distinguishing between these two TIA subtypes may be difficult. In both, attacks may be brief, lasting seconds to minutes, but longer attacks, especially those persisting an hour or more, are not typical of carotid stenosis or occlusion. Multiple attacks are common with both subtypes. The presence or absence of hypertension is not a particularly helpful distinguishing feature; the association in lacunar disease is common but not invariable, and hypertension is only slightly less prevalent in the population with symptomatic large-vessel stenosis. In one recent study of carotid TIAs, the presence of an ipsilateral carotid bruit was a potent indicator of significant and, presumably, symptomatic arterial stenosis.[29] In other studies, however, the incidence of stenosis associated with detectable

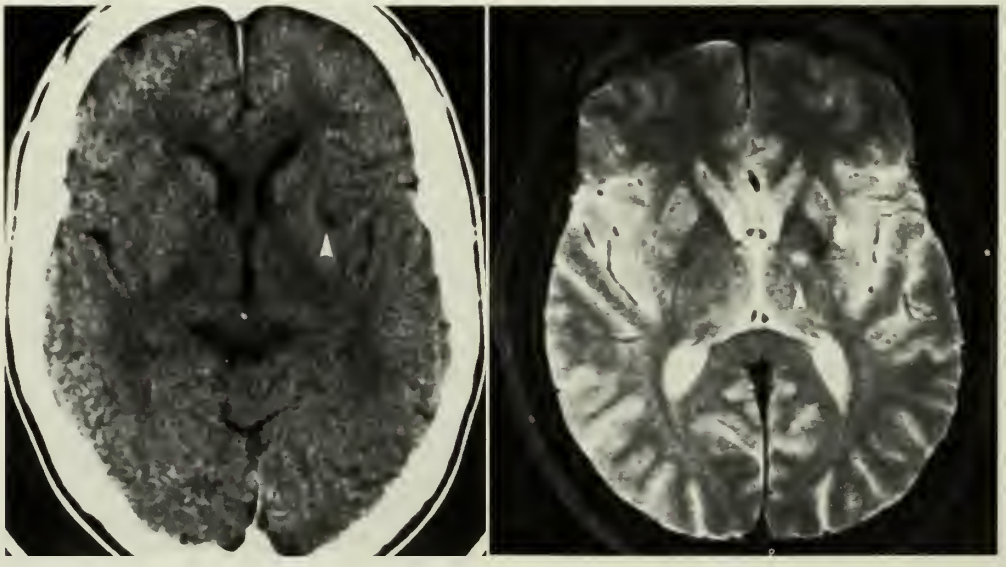


**Figure 1.—Left**, A computed tomographic (CT) scan was done emergently on a patient with repetitive "pure sensory" transient ischemic attacks involving the right hemibody. The arrow indicates a lacuna, presumably old, in the left putamen. **Right**, A magnetic resonance image taken concomitantly with the CT scan shows, in addition to the putaminal lesion seen on CT, a second lacuna in the left thalamus (**arrow**), presumably acute and accounting for the patient's symptoms. Note the signal intensity differences between the two lesions.

carotid bruit has varied from 10% to 85%.[30,40-42] Furthermore, the possibility always exists that anatomic stenosis, although present, is in fact asymptomatic and merely a marker of generalized atherosclerotic disease, with a patient's TIAs the result of another, coexisting process.

A patient's symptom complex may be helpful in establishing a lacunar cause of the attacks. There are certain clinical presentations that strongly suggest lacunar ischemia, specifically "pure motor," "pure sensory" and "dysarthria/clumsy hand." In a study of crescendo TIAs, cerebral angiography done on patients presenting with one of these syndromes showed no evidence of significant stenosis.[33,34] Finally, although brain computed tomography (CT) has not proved particularly useful in the initial evaluation of patients with carotid TIAs,[29,34] magnetic resonance imaging is often helpful in identifying small deep lesions that presumably reflect acute lacunar ischemia (Figure 1).[39]

*Embolic TIAs*

Over the past several years there has been a definite shift in emphasis regarding the importance of embolism in TIA. In the past, many clinicians and clinical researchers embraced the arterial-to-arterial embolization model for TIA and advocated aggressive surgical management of patients with ulcerative lesions.[43,44] Recently, however, there has been an increasing reluctance to recommend a surgical procedure for patients whose carotid angiograms show less than major stenosis, and the practice of using endarterectomy to prevent embolization from an ulcerated lesion is falling out of vogue. Doubtless some percentage of TIAs do occur as a result of embolization from a proximal, ulcerated, nonstenotic atheromatous plaque. That increasing use of endarterectomy has not led to a significant reduction in stroke incidence may be the case but does not necessarily indicate that this embolic model is erroneous or that surgical intervention is of no benefit in TIA management. Regardless, the emphasis on and (perhaps consequently) incidence of arterial-to-arterial embolic TIAs have declined, and many clinicians are opting for medical therapy before endarterectomy (see discussion of treatment below). In general, as opposed to large-vessel stenotic or occlusive TIAs, carotid embolic TIAs are less often multiple and usually persist for longer periods.[19,34] Arterial-to-arterial emboli are felt to be rare in the vertebrobasilar circulation.

A more worrisome source of emboli is the heart. Cardiac emboli appear to cause clinically unmistakable stroke more often than TIA, and the strokes produced are often devastating and unheralded by TIA.[45] Some investigators have reported that, when they occur, cardiogenic embolic TIAs are typically long in duration, persisting an hour or more.[46] A recent study of TIA patients, however, found that most clinical features, including duration and number of attacks, are not helpful in distinguishing between carotid and cardiogenic embolic TIAs.[29,47] Other work suggests that certain types of cardiac disease may predispose to smaller emboli that are more prone to cause TIA or "small stroke" (J.F. Rothrock, MD, S. McAllen, MD, P.D. Lyden, MD, B.J. Taft, unpublished data, May 1986). Even multiple stereotyped attacks or clinical evidence of attacks in several different vascular distributions may not help in establishing a cardiac versus a carotid source. Given this apparent inability to distinguish between cardiac and carotid TIAs on the basis of the clinical presentation alone, many investigators are now suggesting that a cardiac evaluation, including echocardiography and extended arrhythmia monitoring, may be required to exclude a potential cardiac source for emboli even in those patients without a known possible source by history and examination.[47-49] Others have shown a low diagnostic yield from this approach and have concluded that such management is not cost-effective.[50] Our current policy is to use echocardiography and extended cardiac monitoring in all TIA patients with a suspected source of cardiac emboli (by history and examination), in all patients younger than 45 years without another obvious source for TIA and in those patients without a suspected source for cardiac emboli whose TIA presentation cannot be explained by another process (lacunar, carotid atherothrombotic and so forth).

## Arterial Studies

If one is unable to exclude a large-vessel source for TIA with confidence on clinical grounds alone, cerebral angiography may be required. In assessing the results of carotid angiography, one should be cautious not to overestimate the significance of the anatomic disease shown. While a 50% stenosis of the internal carotid artery may produce a pressure gradient across the area of obstruction, more severe stenosis is required to reduce blood flow distally in the cerebral microcirculation.[51] Stenoses involving less than 75% of the vessel lumen are unlikely to cause distal ischemia on a proximal flow-reduction basis, and to assume otherwise may result in misdiagnosis and inappropriate therapy. On the other hand, if angiography reveals severe stenosis in a presumably symptomatic large vessel and the clinical presentation is reasonably consistent with a large-vessel source for the TIAs, therapeutic intervention is indicated (see discussion of treatment).

In some instances, especially when the primary purpose of angiography is to rule out severe stenosis of the proximal internal or common carotid, carotid noninvasive testing (CNIT) may prove an adequate substitute for angiography. CNIT, especially when flow techniques are combined with real-time ultrasound imaging, has become a sensitive and specific means of safely evaluating the carotid bifurcation for obstructive disease and has largely supplanted digital intravenous subtraction angiography.[52] To evaluate the vertebrobasilar and intracranial vasculature, however, and to confidently exclude both total occlusion and nonstenotic ulcerative disease at the carotid bifurcation, CNIT is not yet sufficient, and conventional arteriography remains the procedure of choice. In addition, even when CNIT shows severe carotid stenosis, most surgeons are unwilling to operate without cerebral arteriography, fearing a false-positive study or distal intracranial stenosis ("tandem stenosis") not detected by CNIT.

With continued refinement of cerebral arteriography, including widespread adoption of the digital arterial technique, outpatient arteriography is now available at some centers and appears to be safe, diagnostically adequate and cost-effective.[53]

## Vertebrobasilar TIA

Early TIA studies stressed the benignity of vertebrobasilar attacks relative to those in the carotid distribution.[4,5,8,9] If rigid diagnostic criteria are maintained, however, and isolated vertigo, "dizziness," syncope and other nonspecific symptoms are excluded from study, stroke risk appears similar for carotid and vertebrobasilar TIAs.[10-12] Arterial-to-arterial emboli are felt to be rare in the vertebrobasilar system,

but, otherwise, mechanisms of TIA and stroke are similar to those in the carotid circulation. Occlusion of small penetrating branches off the basilar and posterior cerebral arteries may produce lacunar ischemia, and obstruction of the vertebral or basilar arteries, or one of their major branches, may produce major stroke. Progressive basilar thrombosis is a particularly dangerous situation and may initially present with transient neurologic signs and symptoms—diplopia, ptosis, dysarthria, dysphagia, vertigo, "alternating" numbness and weakness, ataxia—in 40% to 60% of cases.[13,54] We have as yet no treatment of proven benefit for this condition, but many feel that immediate anticoagulation may prevent propagation of basilar intraluminal thrombus, avoiding occlusion of penetrating vessels and the basilar artery itself. While this treatment may help stabilize a precarious clinical situation, it remains uncertain how long anticoagulation therapy should be continued.

Because of the dangers inherent in using heparin in patients with acute cerebral ischemia, some investigators recommend obtaining angiographic confirmation of preocclusive vertebral or basilar stenosis (or both) before treatment is initiated,[13] whereas many others use anticoagulation more indiscriminately, often without benefit of angiography. Our general policy is to do cerebral arteriography on all patients whose vertebrobasilar ischemic attacks are believed to result from large-vessel stenosis or occlusion. If an appropriate lesion is found by arteriography and there is no contraindication to anticoagulation, intravenous administration of heparin is begun in a dose sufficient to maintain the partial thromboplastin time at between 1½ and 2½ times control. If the patient's condition becomes stable after treatment is begun, anticoagulation therapy (with warfarin sodium) is continued for four to six weeks. If the patient remains asymptomatic for further vertebrobasilar ischemic events over that period, anticoagulation therapy is then stopped and antiplatelet therapy is substituted. Although this therapeutic approach appears logical, confirmation of efficacy awaits a well-designed, prospective, randomized study.

As for other TIA subtypes affecting the vertebrobasilar circulation, there is at present no specific treatment for lacunar ischemia, regardless of the vascular distribution involved. While vertebrobasilar arterial-to-arterial emboli are uncommon, 20% to 25% of cardiogenic cerebral emboli involve the posterior circulation. Treatment guidelines in that clinical setting are similar to those for cardiogenic emboli in the anterior circulation (see discussion of treatment).

## Treatment

### *General*

Before selecting a specific treatment option for a patient with TIA, the relative risk and benefit involved should be weighed. First recall that relatively few TIA patients will experience subsequent stroke that is directly related to the TIA itself, even without medical or surgical intervention. As noted previously, not all TIAs are ominous, and, of those that are, not all may require therapy more specific than attention to and treatment of associated risk factors for stroke and coronary artery disease. Treatment should not invoke an outcome worse than the natural history of the disease. For example, if mortality and significant morbidity risk of arteriography and endarterectomy at a given hospital are in excess of 5%, a treatment-modified prognosis is likely no better and perhaps worse than the natural history of TIA, and such intervention thus makes little sense. Any therapy selected should be appropriate to the specific TIA cause. For example, surgical intervention, with its associated risks, must be avoided in patients whose TIAs are lacunar in origin. Furthermore, even if treatment appears to match the cause, a patient cannot be evaluated and treated in a vacuum. TIA often reflects a more generalized disease, systemic atherosclerosis, and coexisting medical conditions, particularly coronary artery disease, must be carefully considered when deciding on therapy. Myocardial infarction, not stroke, is the most common cause of death after TIA, and an endarterectomy for TIA is pointless if a patient is to suffer a fatal myocardial infarct within the next year or, worse, perioperatively.

### *Medical Treatment*

*Antiplatelet therapy.* Studies from the cardiac literature using platelet antiaggregant therapy with aspirin and dipyridamole have shown benefit in preventing coronary vein graft occlusion and, more pertinently, have indicated a substantial reduction in stroke incidence after myocardial infarction.[55-58] Clinical studies examining the effect of antiplatelet therapy on stroke incidence after TIA, however, have yielded conflicting results. While the larger studies have generally indicated benefit from aspirin therapy,[59-61] other studies have failed to confirm this,[62(p30),64] and little has emerged to support the use of dipyridamole in noncardiogenic TIA.[61,65] Several studies have noted aspirin-associated stroke reduction only in men with TIA,[59,60,62] but others have failed to confirm this sex-related response difference.[61] While these inconsistencies are discouraging, it seems reasonable to conclude that antiplatelet therapy may be beneficial for at least some TIA patients and that the studies done to date have simply not been adequately designed to identify this subpopulation.

We tend to recommend aspirin therapy in the following situations:

- *For patients whose ischemic attacks are believed to result from arterial-to-arterial platelet emboli from a nonstenotic, ulcerated, atherosclerotic carotid plaque.* Most investigators maintain that this is the patient group best suited for antiplatelet therapy.
- *For patients with presumed arterial-to-arterial emboli in the presence of significant carotid stenosis who refuse a surgical procedure or who are otherwise not candidates for endarterectomy.* There are some data to support the use of anticoagulants for the first one or two months in these patients, with a subsequent change to antiplatelet therapy if the patient remains asymptomatic.[66]
- *For patients presenting with embolization as a result of mitral valve prolapse*, if there is no echocardiographic evidence of valvular thrombus, severe myxomatous degeneration or other conditions with high embolic potential. In most cases, we begin antiplatelet therapy with aspirin after an initial four- to six-week course of anticoagulant therapy. If these patients experience recurrent emboli while on antiplatelet therapy, anticoagulant therapy is restarted (see "Anticoagulant therapy" below).
- *For patients with presumed lacunar TIA and stroke.* This represents an arbitrary choice, as no study to date has evaluated the efficacy of antiplatelet therapy in this clinical setting.
- *For patients with vertebrobasilar ischemic attacks*

*whose angiograms show no evidence of large-vessel thrombosis.* All patients with vertebrobasilar attacks who are not candidates for anticoagulation are similarly treated, regardless of angiographic findings. In those patients with large-vessel thrombosis who are initially treated with anticoagulation, antiplatelet therapy is substituted for warfarin after six weeks if the patient has remained asymptomatic (see "Anticoagulant therapy" below).

• *For patients who have remained asymptomatic for embolic complications for three months following placement of biosynthetic mitral or aortic prostheses*, aspirin and dipyridamole are substituted for the anticoagulation therapy begun postoperatively.

• With some trepidation and the understanding that clear evidence of benefit has not been established, we begin aspirin therapy in *patients with carotid or vertebrobasilar TIAs of unknown cause.*

Questions have arisen regarding which is the best antiplatelet agent or combination of agents to choose and what dose is optimal. The major TIA studies that have shown benefit from aspirin therapy have used relatively high doses, ranging from 900 mg to 1,300 mg a day, but there is indirect evidence that much lower doses of aspirin may be as or more effective.[67] Results from a large-scale study in the United Kingdom evaluating the use of high-dose versus low-dose aspirin will be available soon and should help resolve this issue. As regards other antiplatelet medications currently in use, dipyridamole and sulfinpyrazone have been studied for their efficacy in stroke prophylaxis, but there is as yet little to support using either medication, alone or in combination with aspirin, for patients with noncardiogenic TIAs.[60,61,65] In theory, dipyridamole combined with low-dose aspirin should be synergistic in opposing platelet aggregation,[68] and future studies may show that this combination has clinical efficacy. At this point, exclusive of clinical research protocols, we can strongly recommend using dipyridamole only in the setting of embolization prophylaxis with prosthetic cardiac valves.[69-71]

Finally, it is important to stress that no medication, including aspirin, will be universally effective for all TIA patients, and an attitude of complacency toward an aspirin-treated patient who is (so far) asymptomatic for recurrent cerebral ischemic attacks should be avoided.

*Anticoagulant therapy.* As has been the case with the antiplatelet agents, data from studies evaluating the effectiveness of anticoagulant therapy for stroke prevention after TIA have been inconsistently encouraging at best.[1,3,72-76] Furthermore, against the uncertain benefit derived from anticoagulation therapy, short or long term, must be weighed the risk of hemorrhagic complications, a particular problem in elderly patients treated on a long-term basis,[74,77-80] although some investigators have reported a low risk in patients so treated.[81-85] For cerebrovascular disease in general, prophylactic anticoagulant therapy for asymptomatic patients is considered to be of definite benefit in relatively few situations, all involving patients with cardiac conditions strongly predisposing to embolic complications—moderate or severe rheumatic valvular disease with or without atrial fibrillation, recent large myocardial infarction and prosthetic valves.[86] Some researchers have suggested that immediate anticoagulation is beneficial for most, if not all, patients with acute, nonseptic, cardiogenic embolic stroke or TIA, specifically in terms of preventing early recurrent emboli.[81,82] Others have warned against this approach, citing an unacceptably high risk of cerebral hemorrhagic complications,[78] especially in patients with large acute infarctions.[87] Although advocated by some and used by many, there are even less hard data to support anticoagulant therapy for such nonspecific conditions as "crescendo TIAs," "progressive stroke" and "stroke in evolution." In cases of TIA, our recommendations for anticoagulant use are as follows:

• Immediate anticoagulation is recommended for patients with suspected nonseptic cardiogenic embolic TIA or small stroke, regardless of the predisposing cardiac condition, if CT shows no significant hemorrhage. Such treatment presumably reduces the incidence of early recurrent cardiogenic emboli, without imposing the unduly high risk of cerebral hemorrhagic complications that may be seen in patients with large embolic strokes. The subsequent need for and optimal duration of ongoing treatment with anticoagulants has not been well established. Decisions regarding this should be made with consideration to the patient's underlying cardiac condition and its potential for chronic embolus production, balanced against the risk of hemorrhagic complications from long-term warfarin therapy in that person.

• Immediate anticoagulation is recommended for patients whose TIAs presumably result from acute or impending large-vessel occlusion, carotid or vertebrobasilar. This represents emergency "best guess" treatment, to be used only until angiography can be done to confirm or deny the clinical impression. If angiography does show severe atherothrombotic stenotic or occlusive disease in the symptomatic large vessel, but surgical intervention is not possible for one reason or another, anticoagulation therapy is continued during the initial period and for four to six weeks thereafter. Even if the patient's condition stabilizes on this treatment, however, there is little to support continued anticoagulant therapy beyond the first month after the initial presentation. If angiography fails to show a clinically appropriate large-vessel lesion, it is difficult to justify continuing anticoagulants, for either the short or the long term.

• Initial anticoagulation is recommended for patients with carotid or vertebral arterial dissections. When TIAs occur as a result of intimal tearing and thrombus formation from neck trauma, significant or trivial, immediate anticoagulation may help to prevent propagation of intraluminal thrombus and embolization to distal intracerebral branches.[88] The optimal duration of such therapy is unknown but should probably not exceed six weeks.

While there may be other situations involving cerebral ischemic attacks where anticoagulants are helpful, these remain to be identified. As was the case with antiplatelet therapy, there is little "magic" about anticoagulation in cases of ischemic stroke and TIA, and randomly applying this therapy will benefit few and possibly harm many.

*Other.* The search continues for medical agents that will prevent or reverse ischemic damage in patients with acute stroke and TIA. Fibrinolytic agents—urokinase, streptokinase and now tissue plasminogen activator—are being evaluated for their efficacy in restoring blood flow and function to brain tissue rendered ischemic by acute thrombosis or embolization.[89-91] Volume expansion therapy and hemodilution may improve the outcome in some patients by increasing cardiac output and reducing blood viscosity.[92,93] Pentoxifylline is under study for its possible value in improving blood flow in the cerebral microcirculation by increasing erythrocyte deformability and thus reducing viscosity.[94] Barbiturate-in-

duced coma has been used for patients with acute cerebral ischemia in hopes of providing "pharmacologic protection" by reducing cerebral metabolic demands.[95] Aminophylline, epoprostenol (prostacyclin), artificial blood substitutes (Fluosol), vasopressors, calcium antagonists and naloxone have all also been studied for their effects on improving outcome in patients with acute stroke and TIA.[96-100]

Until new, more compelling evidence is available, all of the medical therapies just listed should be considered experimental, with their use best left to clinical research centers where they may be studied within experimental protocols. There are, however, some basic principles of medical treatment for TIA that deserve mention. First, ischemia may induce focal loss of cerebral autoregulation, and blood flow to the area of brain involved will be particularly sensitive to any rise and fall in systemic blood pressure and cardiac output. Dehydration and relative hypotension should be avoided in a patient with an acute cerebral ischemic attack; alternatively, TIAs complicating acute, malignant hypertension may respond to the judicious lowering of blood pressure. Second, while the benefits of hemodilution are uncertain in patients whose hematocrits fall in the normal range, notable polycythemia may lead to "sludging" in small intracerebral vessels, and phlebotomy with volume replacement may improve the outcome in patients whose neurologic symptoms are likely a result of this process.

*Surgical Treatment*

Despite widespread and increasing use of carotid endarterectomy for stroke prevention, this treatment has never been rigorously evaluated in the TIA population. Even so, one large study suggested some reduction in stroke risk,[101] and there are undoubtedly TIA patients who will benefit from this approach, if perioperative morbidity and mortality can be kept below 5%.

We consider endarterectomy in patients whose TIAs likely result from significant—that is, 75% or more—carotid atherothrombotic stenosis, with or without associated ulceration. The ideal operative candidate is relatively young (younger than 65 years), is free of major cardiac disease or other significant medical illnesses and has angiographic evidence of cerebral atherosclerotic disease largely restricted to the symptomatic carotid artery.

Endarterectomy for patients with carotid ulcerative lesions in the absence of an associated major stenosis is currently viewed with some skepticism. Although stroke risk may be higher in patients with severe ulcerative lesions, data regarding the magnitude of risk (and consequent need for endarterectomy) have been conflicting.[102,103] In most instances, we recommend antiplatelet therapy for TIA patients with nonstenotic, ulcerative carotid lesions. For patients with particularly severe ulcerative disease—that is, ulcers that are widely excavated, multiple or greater than 2 mm in depth—we consider endarterectomy if the clinical presentation appears to match the arterial pathologic process and the patient is not at high surgical risk.

Until recently, transarterial grafting procedures were widely used for patients with TIAs and stenotic or occlusive disease not amenable to endarterectomy. Results of the large-scale cooperative study of extracranial-intracranial bypass operations, however, have shed considerable doubt on the efficacy of this treatment for patients with ischemic attacks.[104] Further investigations may identify selected groups who will benefit from extracranial-intracranial bypass, but at this point this therapy must be used sparingly and with caution, if at all.

## TIA Versus Stroke

The question has arisen whether the inherently arbitrary distinction between TIA and stroke is useful or even accurate.[105] Many clinicians use TIA as if it were a diagnosis in and of itself, failing to seek a specific cause for the ischemic attack and, to the potential detriment of their patients, too often selecting inappropriate therapies. Others regard evidence of a persistent neurologic deficit as a contraindication to any aggressive therapy, an approach with equal potential for disaster. There is increasing evidence that so-called transient ischemic attacks may actually produce cerebral infarction that is not clinically apparent,[38,39,106,107] and at this point there seems little to be gained from distinguishing between TIA and "small stroke" in a patient presenting with acute cerebral ischemic attacks.

## Summary

The following outlines the major points to be emphasized from this review:

- TIA does convey an increased risk of stroke—and death, most often cardiac—particularly over the ensuing six months and especially within the first month. The risk, however, is relatively small.
- Of the various stroke subtypes, antecedent TIA is most common with large-vessel stenotic or occlusive stroke and lacunae.
- With many TIA patients, beyond evaluating for and treating stroke risk factors, one probably cannot further modify the stroke risk with conventional medical and surgical therapies.
- Given the morbidity and mortality associated with many of the conventional therapies, the relatively low risk conveyed by TIA and the probability that randomly applied therapy is often of little or no benefit, many if not most TIA patients might be better off left alone.
- We need to identify the subpopulation of TIA patients who are particularly at risk for stroke and whose risk may be significantly and safely reduced by medical or surgical therapy, or both. The first step in this process lies in accurately determining a specific cause for each patient's symptoms. This necessitates first ruling out other processes that may mimic TIA, next determining which stroke or TIA subtype is involved and, finally, assigning a specific cause within that subtype.

### REFERENCES

1. Fisher CM: Use of anticoagulants in cerebral thrombosis. Neurology (Minneap) 1958; 8:311-332

2. Baker RN, Broward JA, Fang HC, et al: Anticoagulant therapy in cerebral infarction. Neurology (Minneap) 1962; 12:823-835

3. Siekert RG, Whisnant JP, Millikan CH: Surgical and anticoagulant therapy of occlusive cerebral vascular disease. Ann Intern Med 1963; 58:637-641

4. Acheson J, Hutchinson EC: Observations on the natural history of transient cerebral ischaemia. Lancet 1964; 2:871-874

5. Marshall J: The natural history of transient ischaemic cerebrovascular attacks. Q J Med 1964; 33:309-324

6. Pearce JMS, Gubbay SS, Walton JN: Long-term anticoagulant therapy in transient cerebral attacks. Lancet 1965; 1:6-9

7. Baker RN, Ramseyer JC, Schwartz WS: Prognosis in patients with transient cerebral ischemic attacks. Neurology (Minneap) 1968: 18:1157-1165

8. Freidman GD, Wilson WS, Mosier JM, et al: Transient ischemic attacks in a community. JAMA 1969; 210:1428-1434

9. Ziegler DK, Hassanein RS: Prognosis in patients with transient ischemic attacks. Stroke 1973; 4:666-673

10. Cartlidge NF, Whisnant JP, Elevback LR: Carotid and vertebral-basilar transient cerebral ischemic attacks—A community study, Rochester, Minnesota. Mayo Clin Proc 1977; 52:117-120

11. Toole JF, Yuson CP, Janeway R, et al: Transient ischemic attacks: A prospective study of 225 patients. Neurology (Minneap) 1978; 28:746-753

12. Muuronen A, Kaste M: Outcome of 314 patients with transient ischemic attacks. Stroke 1982; 13:24-31

13. Duncan GW, Pessin MS, Mohr JP, et al: Transient cerebral ischemic attacks. Adv Intern Med 1976; 21:1-20

14. Mendelowitz DS, Kimmins S, Evans WE: Prognosis of patients with transient ischemic attacks and normal angiograms. Arch Surg 1981; 116:1587-1591

15. Harrison MJG, Marshall J: Prognostic significance of severity of carotid atheroma in early manifestations of cerebrovascular disease. Stroke 1982; 13:567-569

16. Heyman A, Gore T, Wilkinson WE, et al: TIA with benign outcome. Stroke 1982; 13:112

17. Landi G, Guidotti M, Pinciroli D, et al: Reversible ischemic attacks with normal angiogram: Risk factors, clinical findings, and prognosis. Neurology (NY) 1985; 35:412-415

18. Toole JF, Yuson CP: Transient ischemic attacks with normal arteriograms: Serious or benign prognosis? Ann Neurol 1977; 1:100-102

19. Rothrock JF, Lyden PD: Unstable carotid artery syndrome: Clinical management and outcome. Stroke 1985; 16:140

20. Pessin MS, Duncan GW, Mohr JP, et al: Clinical and angiographic features of carotid transient ischemic attacks. N Engl J Med 1977; 296:358-362

21. Harrison MJG, Marshall J, Thomas DJ: Relevance of duration of transient ischaemic attacks in carotid territory. Br J Med 1978; 1:1578-1579

22. Marshall J, Meadows S: The natural history of amaurosis fugax. Brain 1968; 91:419-434

23. Hooshmand H, Vines FS, Lee HM, et al: Amaurosis fugax: Diagnostic and therapeutic aspects. Stroke 1974; 5:643-647

24. Eisenberg RL, Mani RL: Clinical and arteriographic comparison of amaurosis fugax with hemispheric transient ischemic attacks. Stroke 1978; 9:254-255

25. Poole CM, Russell RW: Mortality and stroke after amaurosis fugax. J Neurol Neurosurg Psychiatry 1985; 48:902-905

26. Mohr JP: The Harvard Cooperative Stroke Registry: A prospective registry. Neurology (Minneap) 1978; 28:754-762

27. Humphrey PD, Marshall J: Asymptomatic strokes with recovery: Prognosis and investigation. Stroke 1981; 12:765-769

28. Tsuda Y, Kimura K, Yoneda S, et al: CBF and $CO_2$ reactivity in transient ischemic attacks due to internal carotid occlusion and internal carotid mild stenosis. Neurol Res 1983; 5:17-37

29. Bogousslavsky J, Hachinski VC, Boughner DR, et al: Clinical predictors of cardiac and arterial lesions in carotid transient ischemic attacks. Arch Neurol 1986; 43:229-233

30. Ramirez-Lassepas M, Sandok BA, Burton RC: Clinical indicators of extracranial carotid artery disease in patients with transient symptoms. Stroke 1973; 4:537-540

31. Lemak NA, Fields WS: The reliability of clinical predictors of extracranial artery disease. Stroke 1976; 7:377-378

32. Adams HP, Putnam SF, Corbett JJ, et al: Amaurosis fugax: The results of arteriography in 59 patients. Stroke 1983; 14:742-744

33. Rothrock JF, Lyden PD: Unstable carotid artery syndrome: Predictive criteria. Circulation 1984; 70(Suppl II):136

34. Rothrock JF, Lyden PD, Yee J, et al: Unstable carotid artery syndrome: Clinical management, risks and outcome. Vasc Surg, in press

35. Fisher CM: The arterial lesions underlying lacunes. Acta Neuropathol (Berlin) 1968; 12:1-15

36. Miller VT: Lacunar stroke—A reassessment. Arch Neurol 1983; 40:129-134

37. Fisher CM, Curry HB: Pure motor hemiplegia of vascular origin. Neurology (Minneap) 1965; 13:30-44

38. Perrone P, Candelise L, Scotti G, et al: CT evaluation in patients with transient ischemic attack. Eur Neurol 1979; 18:217-221

39. Rothrock JF, Hesselink JR: Utility of MRI *vs* CT in acute lacunar disease. Stroke 1986; 17:134

40. Ziegler DK, Zileli T, Dick A, et al: Correlation of bruits over the carotid artery with angiographically demonstrated lesions. Neurology (Minneap) 1971; 21:860-865

41. Veda K, Toole JF, McHenry L: Carotid and vertebrobasilar transient ischemic attacks: Clinical and angiographic correlation. Neurology (Minneap) 1979; 29:1094-1101

42. Grotta JC, Bigelow RW, Hu H, et al: The significance of carotid stenosis or ulceration. Neurology (NY) 1984; 34:437-442

43. Moore WS, Hall AD: Ulcerated atheroma of the carotid artery—A cause of transient cerebral ischemia. Am J Surg 1968; 116:237-242

44. Moore WS, Hall AD: Importance of emboli from carotid bifurcation in pathogenesis of cerebral ischemic attacks. Arch Surg 1970; 101:708-716

45. Sherman DG, Goldman L, Whiting RB, et al: Thromboembolism in patients with atrial fibrillation. Arch Neurol 1984; 41:708-710

46. Harrison MJG, Marshall J: Atrial fibrillation, TIAs, and completed strokes. Stroke 1984; 15:441-442

47. Bogousslavsky J, Hachinski VC, Boughner DR, et al: Cardiac and arterial lesions in carotid transient ischemic attacks. Arch Neurol 1986; 43:223-228

48. Rem JA, Hachinski VC, Boughner DR, et al: Value of cardiac monitoring and echocardiography in TIA and stroke patients. Stroke 1985; 16:950-956

49. Biller J, Adams HP, Johnson M, et al: Echocardiographic evaluation of young adults with nonhemorrhagic cerebral infarction. Stroke 1986; 17:140

50. Come PC, Riley M, Bivas NK: Roles of echocardiography and arrhythmia monitoring in the evaluation of patients with suspected systemic embolism. Ann Neurol 1983; 13:527-531

51. Brice JG, Dowsett DJ, Lowe RD: Hemodynamic effects of carotid artery stenosis. Br Med J 1964; 2:1363-1366

52. Fischer GC, Anderson DC, Farber R, et al: Prediction of carotid disease by ultrasound and digital subtraction angiography. Arch Neurol 1985; 42:224-227

53. Seeger JF, Yang PJ, Bernhard VM, et al: Outpatient cerebral angiography—A prospective study. Stroke 1986; 17:146

54. Kubik CS, Adams RD: Occlusion of the basilar artery—A clinical and pathologic study. Brain 1946; 69:73-121

55. Chesebro JH, Clements IP, Fuster V, et al: A platelet-inhibitor drug trial in coronary bypass operations—Benefit of perioperative dipyrimadole and aspirin therapy on early postoperative vein-graft patency. N Engl J Med 1982; 307:73-78

56. Chesebro JH, Clements IP, Fuster V: Benefit of perioperative dipyrimadole plus aspirin therapy for late postoperative aortocoronary vein graft patency. Circulation 1982; 66(Suppl II): 94

57. Aspirin Myocardial Infarction Study Research Group: A randomized controlled trial of aspirin in persons recovered from myocardial infarction. JAMA 1980; 243:661-669

58. The Persantine-Aspirin Reinfarction Study Research Group: Persantine and aspirin in coronary heart disease. Circulation 1980; 62:449-461

59. Fields WS, Lemak NA, Frankowski RF, et al: Controlled trial of aspirin in cerebral ischemia. Stroke 1977; 8:301-316

60. The Canadian Cooperative Study Group: A randomized trial of aspirin and sulfinpyrazone in threatened stroke. N Engl J Med 1978; 229:53-59

61. Bousser MG, Eschwege M, Haguenau JM, et al: 'AICLA' controlled trial of aspirin and dipyridamole in the secondary prevention of atherothrombotic cerebral ischemia. Stroke 1983; 14:5-14

62. Candelise L, Landi G, Perrone P, et al: The anturane transient ischemic attacks Italian study, *In* Cerebrovascular Diseases: New Trends in Surgical and Medical Aspects (Supp). Amsterdam, Elsevier/North Holland, 1981

63. Guiraud-Chaumeil B, Rascol A, David J, et al: Prévention des récidives des accidents vasculaires cérébraux ischémiques par les anti-agrégants, plaquettaires—Résultats d'un essai thérapeutique contrôlé de 3 ans. Rev Neurol (Paris) 1982; 138:367-385

64. Sorenson PS, Pederson H, Marquardsen J, et al: Acetylsalicylic acid in the prevention of stroke in patients with reversible cerebral ischemic attacks—A Danish Cooperative Study. Stroke 1983; 14:15-22

65. Acheson J, Danta G, Hutchinson EC: Controlled trial of dipyridamole in cerebral vascular disease. Br Med J 1969; 1:614-615

66. Olsson JE: Anticoagulant vs antiplatelet therapy as prophylactic against cerebral infarction in transient ischemic attacks. Stroke 1980; 11:4-9

67. Weksler BB, Kent JL, Rudolf D, et al: Effects of low dose aspirin on platelet function in patients with recent cerebral ischemia. Stroke 1985; 16:5-9

68. Harker LA, Slichter SJ, Sauvage LR: Platelet consumption by arterial prosthesis: The effects of endothelialization and pharmacologic inhibition of platelet function. Ann Surg 1977; 186:594-601

69. Sullivan JM, Harken DE, Gorlin R: Effect of dipyridamole on the incidence of arterial emboli after cardiac valve replacement. Circulation 1969; (Suppl I):149-153

70. Sullivan JM, Harken DE, Gorlin R: Pharmacologic control of thromboembolic complications of cardiac-valve replacement. N Engl J Med 1971; 25:1391-1394

71. Chesebro JH, Fuster V, Elveback LR, et al: Trial of combined warfarin plus dipyridamole or aspirin therapy in prosthetic heart valve replacement: Danger of aspirin compared with dipyridamole. Am J Cardiol 1983; 51:1537-1541

72. Whisnant JP, Matsumoto N, Elveback LR: The effect of anticoagulant therapy on the prognosis of patients with transient cerebral ischemic attacks in a community. Mayo Clin Proc 1973; 48:844-848

73. Olsson JE, Miller R, Berneli S: Long-term anticoagulant therapy for TIAs and minor strokes with minimum residuum. Stroke 1976; 7:444-451

74. Whisnant JP, Cartlidge NF, Elveback LR: Carotid and vertebral-basilar transient ischemic attacks: Effect of anticoagulants, hypertenson and cardiac disorders on survival and stroke occurrence—A population study. Ann Neurol 1978; 3:107-115

75. Olsson JE, Brechter C, Backlund H, et al: Anticoagulant vs prophylactic against cerebral infarction in transient ischemic attacks. Stroke 1980; 11:4-9

76. Buren A, Ygge J: Treatment program and comparison between anticoagulants and platelet aggregation inhibitors after transient attack. Stroke 1981; 12:578-580

77. Wintzen AR, deJonge H, Loeliger EA, et al: The risk of intracerebral hemorrhage during oral anticoagulant treatment: A population study. Ann Neurol 1984; 16:553-558

78. Shields RW, Laureno R, Lachman T, et al: Anticoagulant-related hemorrhage in acute cerebral embolism. Stroke 1984; 15:426-437

79. Calandre L, Ortega JF, Bermejo F: Anticoagulation and hemorrhagic infarction in cerebral embolism secondary to rheumatic heart disease. Arch Neurol 1984; 41:1152-1154

80. Levine M, Hirsh J: Hemorrhagic complications of long-term anticoagulant therapy for ischemic cerebral vascular disease. Stroke 1986; 17:111-116

81. Furlan AJ, Cavalier SJ, Hobbs RE, et al: Hemorrhage and anticoagulation after nonseptic embolic brain infarction. Neurology (NY) 1982; 32:280-282

82. Koller RL: Recurrent embolic cerebral infarction and anticoagulation. Neurology (NY) 1982; 32:283-285

83. Lodder J, van der Lugt PJM: Evaluation of the risk of immediate anticoagulant treatment in patients with embolic stroke of cardiac origin. Stroke 1983; 14:42-45

84. Martin GJ, Biller J: Nonseptic cerebral emboli of cardiac origin. Arch Intern Med 1984; 144:1997-1999

85. Bogousslavsky J, Regli F: Anticoagulant-induced intracerebral bleeding in brain ischemia. Acta Neurol Scand 1985; 71:464-471

86. Easton JD, Sherman DG: Management of cerebral embolism of cardiac origin. Stroke 1980; 11:433-440

87. Cerebral Embolism Study Group: Immediate anticoagulation of embolic stroke: Brain hemorrhage and management options. Stroke 1984; 15:779-789

88. Hart RG, Easton JD: Dissections. Stroke 1985; 16:925-927

89. Centeno RS, Hackney DB, Rothrock JR: Streptokinase clot lysis in acute occlusions of the cranial circulation: Semiquantitative analysis in rabbit models. AJNR 1985; 6:589-594

90. DelZopo GJ, Copeland BR, Waltz TA, et al: Thrombolytic therapy in a baboon model of acute stroke. Stroke 1986; 17:133

91. Zivin J, Fisher M, DeGirolami U, et al: Tissue plasminogen activator for embolic stroke. Stroke 1986; 17:133

92. Wood JH, Fleischer AS: Observations during hypervolemic hemodilution of patients with acute focal cerebral ischemia. JAMA 1982; 248:2999-3004

93. Strand T, Apslund K, Eriksson S, et al: A randomized controlled trial of hemodilution therapy in acute ischemic stroke. Stroke 1984; 15:980-989

94. Herskovits E, Vazquez A, Famulari A, et al: Randomised trial of pentoxifylline versus acetylsalicyclic acid plus dipyridamole in preventing transient ischaemic attacks. Lancet 1981; 1:966-968

95. Agnoli A, Palene N, Ruggieri S, et al: Barbiturate treatment of acute stroke. Adv Neurol 1979; 25:269-274

96. Britton M, DeFaire U, Helmers C, et al: Lack of effect of theophylline on the outcome of acute cerebral infarction. Acta Neurol Scand 1980; 62:116-123

97. Miller VT, Coull BM, Yatsu FM, et al: Prostacyclin infusion in acute cerebral infarction. Neurology (NY) 1984; 34:1431-1435

98. Oda Y, Murata T, Uchida Y, et al: Clinical evaluation of artificial blood substitute (Fluosol-DA 20%) in patients of cerebral ischemia. No Shinkei Geka [Neurol Res] 1982; 10:637-644

99. Gelmers HJ, Gorter K, deWeerdt JA: Effect of nimodipine on clinical outcome in patients with acute ischemic stroke. Stroke 1986; 17:145

100. Estanol B, Aguilar F, Corona T: Diagnosis of reversible versus irreversible cerebral ischemia by the intravenous administration of naloxone. Stroke 1985; 16:1006-1009

101. Fields WS, Maslenikov V, Meyer JS, et al: Joint Study of Extracranial Arterial Occlusion: A cooperative study. JAMA 1970; 211:1993-2003

102. Moore WS, Boren C, Malone JM, et al: Natural history of nonstenotic, asymptomatic ulcerative lesions of the carotid artery. Arch Surg 1978; 113:1352-1359

103. Harward TRS, Kroener JM, Wickbom IG, et al: Natural history of asymptomatic ulcerative plaques of the carotid bifurcation. Am J Surg 1983; 146:208-212

104. Failure of extracranial-intracranial arterial bypass to reduce the risk of ischemic stroke: Results of an international randomized trial. N Engl J Med 1985; 313:1191-1200

105. Caplan LR: Are terms such as completed stroke or RIND of continued usefulness? Stroke 1983; 14:431-433

106. Waxman S, Toole J: Temporal profile resembling TIA in the setting of cerebral infarction. Stroke 1983; 14:433-437

107. Bogousslavsky J, Regli F: Cerebral infarct in apparent transient ischemic attack. Neurology 1985; 35:1501-1503

# Medical Staff Conference

## Current Concepts in the Treatment of Tuberculosis

*These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs Homer A. Boushey, Associate Professor of Medicine, and David G. Warnock, Associate Professor of Medicine, under the direction of Dr Lloyd H. Smith, Jr, Professor of Medicine and Associate Dean in the School of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, School of Medicine, San Francisco, CA 94143.*

RICHARD K. ROOT, MD:* *Tuberculosis remains an active and important health problem for Americans. The influx of immigrants from Southeast Asia and Central and South America has focused attention on the high endemic rates of tuberculosis in these populations and the problem of resistance to first-line antituberculous therapy. This timely review provides a rationale and guidelines for "short-course" therapy for tuberculosis that keeps these concerns in mind.*

*Dr Tager is an Associate Professor of Medicine at the University of California, San Francisco (UCSF), and is based at the San Francisco Veterans Administration Medical Center. He has a distinguished record of accomplishment in the study of epidemiologic mechanisms in infectious diseases.*

IRA B. TAGER, MD, MPH:† In this review I intend to summarize a conceptual framework of how major antituberculous drugs are used in modern, short-course chemotherapy and to provide a classification of the behavior of these drugs that will be useful, in a generic way, for designing therapeutic regimens for tuberculosis. I will also describe some selected applications of recent knowledge to the design of chemotherapeutic regimens.

Before presenting specific aspects of antituberculous therapy, a few general comments about the tubercle bacillus are necessary. The tubercle bacillus is an obligate aerobic bacterium that is capable of growing both intracellularly and extracellularly. The organism has a very long average replication time, approximately 20 hours, when studied in vitro.[1] In biologically relevant situations, in both animal and human tuberculosis, a very wide range of replication times, from rapid to dormant states, can be observed. This characteristic of the tubercle bacillus is important in the understanding of how chemotherapeutic regimens are designed.

Drug resistance occurs in virtually all populations of tubercle bacilli that have not been exposed to antituberculous drugs.[1,2] The appearance of such natural resistance is largely a statistical phenomenon based on the population density of the organism, the probabilities of which differ somewhat for the different drugs (Table 1). This fact was recognized very early,[3] and prevention of the emergence of drug-resistant organisms is one of the reasons why antituberculous chemotherapy, almost from its inception, has been based on the use of more than one drug.

Finally, by way of introduction, several terms require definition. Evaluation of the bactericidal activity of antituberculous drugs in vivo, in contrast to in vitro assessment, refers to the degree of killing of organisms as assessed over the first two days of therapy in an animal model or in disease in humans. The bactericidal activity of the drugs is distinguished from another characteristic called the "sterilizing activity" of the drug, which is defined as the ability of the drug to kill all tubercle bacilli as rapidly as possible. It is this latter characteristic of the drugs that is responsible for the ultimate cure of the disease, as will be discussed. In experimental and in clinical situations, the sterilizing capacity of antituberculous drugs is assessed by the evaluation of the rate of conversion to sputum negativity at two months of therapy and by relapse rates that follow the conclusion of therapy, generally, in the case of humans, over the first three years after therapy has been completed.

Figure 1[4] presents a simplified working model of how antituberculous drugs work in complex biologic systems. This model defines the idealized tuberculous lesion as having three components—not necessarily physically separated from each other, but constituting a complex lesion. One component is the cavitary lesion, characterized by large bacterial populations, generally in the range of $10^7$ to $10^9$ organisms[4]; this lesion, therefore, represents the population out of which naturally occurring drug resistance is most likely to emerge. Organisms in this population tend to be actively growing. The pH environment tends to be neutral or alkaline (the importance of which will become evident during the discussion of the behavior of the drugs). A second element of the model is the closed caseous lesion, which is believed to have a population in the range of $10^4$ to $10^5$ organisms.[3] Metabolically, these organisms are slowly or only intermittently growing and, in some cases, may be dormant. In the initial conceptualization of this model, which will be presented in modified form subsequently, it was thought that the caseous component represented a uniformly neutral pH environment. The final part of the ideal lesion is the intracellular component, the pulmonary macrophage population, made up of about $10^4$ to $10^5$ slowly replicating organisms. This component is thought to be in an acid environment for reasons that will be presented below.

In the context of the model, failure of therapy relates to two different problems (Figure 2).[1] One problem is failure due to the selection of drug-resistant organisms that occur naturally in the environment and are found in a very discrete, large population of rapidly growing organisms. The second and most common cause of failure is due to the persistence of

*Professor and Chair, Department of Medicine, UCSF School of Medicine.

†Associate Professor of Medicine and Epidemiology, UCSF School of Medicine, and Chief, Infectious Disease Section, Medical Service, Veterans Administration Medical Center, San Francisco.

(Tager IB: Current concepts in the treatment of tuberculosis [Medical Staff Conference]. West J Med 1987 Apr; 146:461-465)

TABLE 1.—*Frequency of Resistant Tubercle Bacilli in Populations of Bacteria Unexposed to Antituberculous Drugs*

| Drug | Frequency |
|---|---|
| Isoniazid | $1.5$ to $3.5 \times 10^{-6}$ |
| Streptomycin sulfate | $0.5$ to $4.0 \times 10^{-6}$ |
| Rifampin | $1.0$ to $3.0 \times 10^{-8}$ |
| Ethambutol hydrochloride | $0.5$ to $1.0 \times 10^{-4}$ |

organisms. These "persistors" are metabolically relatively inactive or dormant, and they reside in two separate but somewhat overlapping populations. The design of antituberculous regimens has been predicated on the need to deal with these two sets of population dynamics and their implications for the success or failure of therapy.

Before going on to a discussion of the individual drugs, some of the data that have been used to formulate the metabolic and environmental characteristics of the model in Figure 1 will be reviewed. Quantitative estimates of the bacterial populations in cavitary and caseous lesions have been derived from direct measurements of surgically removed lung tissue.[3] The estimate for the intracellular population is probably the least accurate of the three, but is reasonable, based on early studies on the behavior of pyrazinamide in murine tuberculosis.[5]

Direct measurements of cavitary and caseous lesions have shown that their average pH is about 7 with a range of 6.8 to 7.2.[6] Recent work, to be discussed later, suggests that the caseous lesion is likely, in fact, to be a complex set of microenvironments with small, localized areas of inflammation and relatively low pH. Because the activity of pyrazinamide, a very important drug in modern therapeutic regimens, and the aminoglycosides (such as streptomycin) is pH-dependent,[8] inferences about the pH environments of the model in Figure 1 are of considerable importance. The inference that the bacterial populations in macrophages might be in an acid environment is derived from the knowledge of the way in which pyrazinamide acts. It has little antituberculous activity in vitro at a pH above 5.6,[7,8] but does kill tubercle bacilli within macrophages in in vitro experiments in which the extracellular environment is maintained at pH 7.[9]

Isoniazid and rifampin are two of the mainstays of current therapy, and they illustrate some of the complexities in understanding how antituberculous drugs behave. Both isoniazid and rifampin in vitro have equivalent antituberculous activity[10,11] and they are both active over a broad range of pHs.[10] In vivo, however, isoniazid appears to have a greater early bactericidal activity than rifampin. In patients treated with a single drug as part of their initial therapy,[12] the use of isoniazid leads to about three fourths of a log per day reduction in bacterial counts over the first two days of therapy, whereas that of rifampin results in a reduction somewhat less than a third of that for isoniazid over the first 48 hours of therapy. The effect of adding rifampin to a regimen of other drugs over the first two days is very limited relative to the effect of adding isoniazid. Moreover, additional data from in vitro studies indicate that isoniazid and rifampin actually appear to be antagonistic during the first two days of therapy.[10]

The above findings are completely at odds with the very important role that rifampin has come to have in the therapy for tuberculosis. The explanation for this apparent paradox lies in the fact that isoniazid and rifampin differ fundamentally in the way in which they act on slowly or intermittently replicating organisms, both in vitro and in vivo. Figure 3 illustrates the differences in vitro.[13] Tubercle bacilli were grown in cultures kept regularly at 8°C and intermittently (one to six hours a day) at 37°C. By 15 days, those cultures exposed to rifampin achieved a level of killing of these intermittently growing organisms that was just about achieved at about one month of exposure to isoniazid. Thus, rifampin in vitro is much more rapid in the onset of its activity against these relatively inactive organisms that are thought to be the cause of most of the long-term failures of chemotherapy. This differential effect has been substantiated in vivo also. When mice treated with a regimen of isoniazid and streptomycin sulfate and a one-month course of rifampin are compared with mice treated with a regimen of isoniazid and streptomycin alone,[10] there is an approximate threefold greater reduction in the number of bacteria in the rifampin-treated group after a month of therapy. More important, at four months, three months after the rifampin therapy has been stopped, there is about a 45-fold reduction in the number of persisting organisms in the rifampin-treated mice. This observation supports the fact that rifampin is acting very rapidly on a relatively slow-growing population of organisms that isoniazid therapy alone is not capable of eradicating despite three months of additional therapy. Moreover, 75% of animals given a regimen of isoniazid and streptomycin for tuberculosis for 18 months show lung cultures positive for *Mycobacterium tuber-*

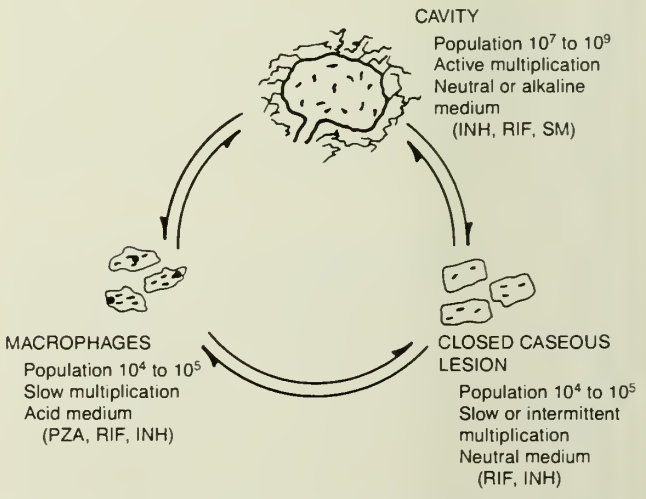



**Figure 1.**—Populations of *Mycobacterium tuberculosis* in a tuberculous host. Drugs in parentheses refer to agents effective against the specific population (from Dutt and Stead,[3] by permission). INH = isoniazid, PZA = pyrazinamide, RIF = rifampin, SM = streptomycin sulfate

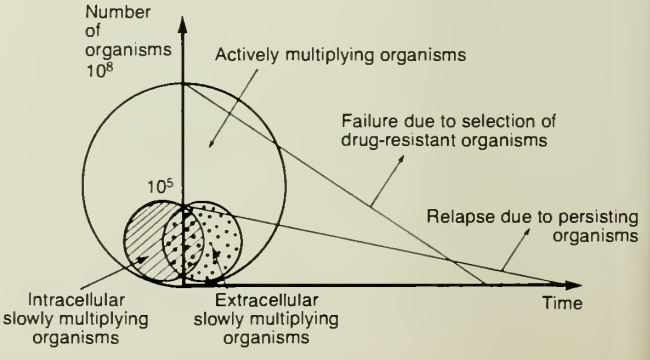



**Figure 2.**—Results of therapy for tuberculosis in relation to the population dynamics of the tubercle bacilli (from Grosset,[1] by permission).

*culosis* three to six months after the cessation of therapy versus 0% for animals treated with a nine-month regimen of isoniazid and rifampin.[1]

Pyrazinamide, as indicated above, is active only in an acid environment,[8] but, like rifampin, it has the unique capacity to rapidly sterilize tuberculous lesions in biologic systems.[5,10] In mice treated with a regimen of isoniazid and streptomycin,[14] 70% of the animals still have positive cultures of their lungs after 12 months of therapy. In pyrazinamide-treated animals, virtually all the lungs are sterilized by 6 months, and by 12 months essentially all of the animals have negative lung cultures. These data also indicate that most of the drug's effect occurs early in the course of therapy. Similarly, in human tuberculosis, pyrazinamide appears to exert its most dramatic effects during the first two months of therapy because adding it during the first two months of multiple drug regimens reduces considerably the relapse rates after the cessation of therapy; continuing the drug therapy beyond two months confers relatively little additional benefit.[14]

The model presented in Figure 1 indicates that pyrazinamide and rifampin act on different populations of bacteria that are dormant or slowly metabolizing and that they are not simply overlapping drugs. Three lines of evidence have been offered to support this concept.[15] Data on the effects of antituberculous drugs on quantitative sputum cultures during the first 14 days of therapy suggest that these two drugs do not possess high early bactericidal activity (fall in colony counts over days 0 to 2 of therapy)[10,12,15]; therefore, their sterilizing activity cannot be explained on this basis. The second line of evidence is that referred to in the preceding paragraph on the behavior of pyrazinamide. The final source of evidence is derived from studies of short-course (four months) chemotherapy for pulmonary tuberculosis.[15] All regimens consisted of two months of initial therapy with streptomycin, isoniazid, rifampin and pyrazinamide. The two regimens that contained rifampin for the subsequent two months had lower relapse rates (14% and 11%) than did the regimens that did not contain rifampin (28% and 30%). Such a result would be very unlikely if both agents were acting on the same population of organisms.

Recently, Mitchison and Nunn[7,16] have reconsidered the model in Figure 1 to better account for data that relate to the behavior of pyrazinamide. If the drug were acting only in an intracellular environment on a small bacterial population, it should have relatively little effect on the total bacterial count during the first 14 days of therapy because that population is very small ($10^4$ organisms in a population of $10^9$ or more organisms). Pyrazinamide, however, is capable of killing 97% of an initial bacterial load over the first two weeks of therapy when used by itself.[12] Additionally, in patients who harbor tubercle bacilli that are resistant to the use of isoniazid only or isoniazid and streptomycin, adding pyrazinamide does lead to therapeutic success in a moderate number of cases.[16] Finally, experimental data provide some support for the possibility that there may be localized areas of inflammation within the caseous lesions that have a pH in the range that is optimal for the activity of pyrazinamide (less than 5.6).[7]

On the basis of the above, the model in Figure 4 has been developed. At the beginning of therapy, the bulk of the population of tubercle bacilli is growing rapidly in an environment at physiologic pH. At this stage, isoniazid is the most active drug, rifampin and streptomycin participate to a lesser extent and, basically, pyrazinamide is inactive. As the bulk of the bacteria is killed and as the host mounts an inflammatory response to the infection, tubercle bacilli are inhibited by the host response and now also find themselves in a pH environment that is much more conducive to the activity spectrum of pyrazinamide. At this point, pyrazinamide and rifampin are capable of killing these slowly growing organisms rather effectively. There is a continual movement of organisms between these two microenvironments in the early stages of the disease. After several weeks, the inflammation tends to subside and a more chronic fibrotic response is seen. Tubercle bacilli again are largely in areas with little acute inflammation (physiologic pH), growing relatively slowly, and, therefore, rifampin becomes the critical drug in the killing of these organisms. The main reason why antituberculous therapy before the advent of rifampin required 18 months rather than the six to nine months used currently is that isoniazid was the only drug available that was capable, over the long term, of killing these relatively metabolically inactive organisms. Because its effect is relatively slow, it had to be given for a long period of time. The same is probably true of pyrazinamide because its ongoing activity depends on the constant cycling of inflammation-no inflammation.

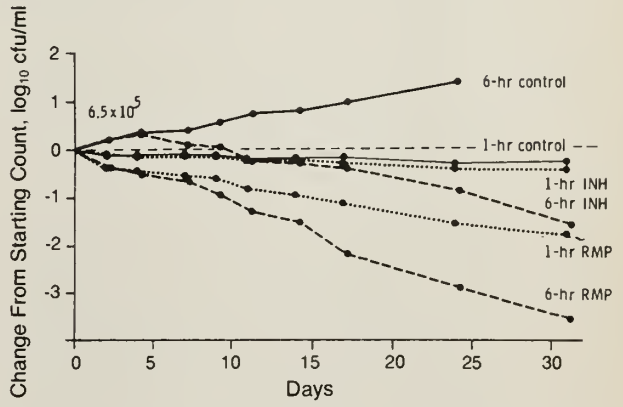



**Figure 3.**—Bactericidal activity of rifampin (RMP) and isoniazid (INH) on cultures of *Mycobacterium tuberculosis* grown at 8°C and exposed on 5 days each week to 37°C for 1 or 6 hours (from Dickinson and Mitchison,[13] by permission). cfu = colony-forming units

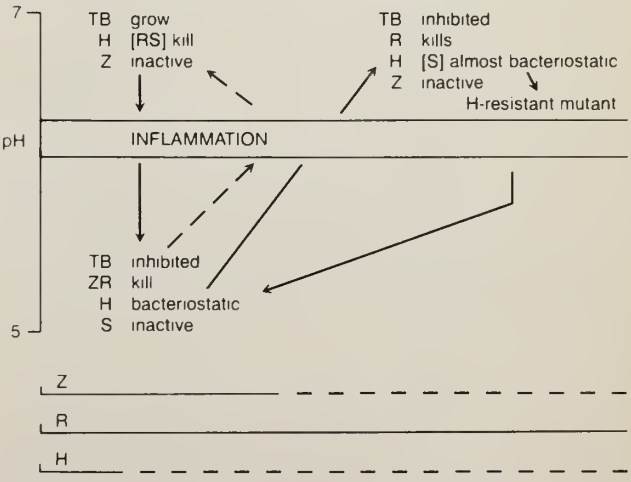



**Figure 4.**—Role of pH and inflammation in modifying the growth of *Mycobacterium tuberculosis* and the action of isoniazid (H), streptomycin (S), rifampin (R) and pyrazinamide (Z) in killing organisms at the start of chemotherapy, during its first weeks and as a result of the growth of resistant tubercle bacilli (TB). The duration of periods of rapid killing (early bactericidal and sterilizing) by Z, R and H is indicated in the lower part (from Mitchison,[7] by permission).

TABLE 2.—*Grading of Antibacterial Drugs Used in the Therapy for Tuberculosis**

| Activity | Sterilizing Activity | Prevention of Drug Resistance | |
|---|---|---|---|
| | | 1st Line Drugs | Reserve Drugs |
| High . . . | Rifampin | Isoniazid | . . . |
| | Pyrazinamide | Rifampin | . . . |
| | Isoniazid | Streptomycin sulfate | Ethionamide |
| | Streptomycin sulfate† | Ethambutol hydrochloride | Cycloserine |
| | Ethambutol hydrochloride | . . . | . . . |
| Low . . . | . . . | Pyrazinamide | Capreomycin sulfate |

*Adapted from Mitchison.[7]
†Capreomycin sulfate, viomycin sulfate, kanamycin sulfate.

Ethambutol hydrochloride is a drug that does not appear as a major chemotherapeutic agent in the models that have been presented. In vitro and in vivo, ethambutol has moderate bactericidal activity.[11] In vitro, when ethambutol is added to isoniazid or rifampin, it adds little to their capacity to kill tubercle bacilli.[7] Most important, ethambutol has little sterilizing capacity. In murine tuberculosis, ethambutol provides no additional sterilizing capacity to that observed for rifampin.[17] In humans, ethambutol also fails to contribute meaningfully to the sterilizing capacity of regimens that contain rifampin or pyrazinamide, or both.[18] At the end of two months of therapy (assessment of sterilizing capability), 90% of the pyrazinamide-treated patients versus 76% of the ethambutol-treated patients have negative cultures. Twelve months after the cessation of therapy, the failure rate for the pyrazinamide regimen is 1.4% and for the ethambutol regimen it is 7.5%.

Based on the data presented, regimens to treat tuberculosis must include agents that are bactericidal against both rapidly and slowly dividing bacteria and that can prevent the emergence of drug-resistant bacilli. All drugs currently in use to treat tuberculosis can be classified with regard to these properties. Such a classification is presented in Table 2. The ability of drugs to prevent the emergence of resistance has been assessed from therapeutic results obtained in patients with severe tuberculosis—that is, large bacterial populations—who were given various combinations of single- and multiple-drug therapy.[10,15]

How do the above concepts thus far apply to the real-world problems of therapy for tuberculosis? The first issue to consider in this regard relates to the minimum duration of therapy required to achieve the high cure rates that have come to be expected from modern tuberculosis therapy. A compilation of data from a large number of studies that have evaluated the success of therapy in patients with smear- and culture-positive tuberculosis with a variety of treatment regimens, all of which included isoniazid and rifampin and most of which included pyrazinamide, shows that the minimum duration of therapy appears to be about five months. For routine situations, where rifampin can be used in therapy, nine months appears to be the maximum duration necessary. In this regard, it is important to note that the combination of isoniazid and rifampin is not satisfactory for durations of therapy that are shorter than nine months.[19] The failure rate of therapy when these two drugs are used alone for six months is 7% to 9%.[19]

Given these data, what are the reasonable choices available for the therapy for tuberculosis? If a nine-month period is considered appropriate, then the regimen of isoniazid and rifampin (given daily for a month, twice a week for eight months) developed by Dutt and co-workers[20] seems to be the most acceptable of the available choices in terms of ease of administration and degree of toxicity. When a six-month duration seems preferable, isoniazid and rifampin alone are not sufficient, but a number of therapeutically equivalent alternatives are available (Table 3). Considerations of patient compliance and cost would seem to favor those regimens that use intermittent dosing intervals.

TABLE 3.—*Six-Month Regimens for Treatment of Tuberculosis**

| Initial/Continuation | Follow-up, Months | % Relapse |
|---|---|---|
| IR | 30 | 8 |
| 2SIRP/4IRP† | 24 | 0 |
| 2SIRP/4IR | 24 | 2 |
| $2SIRP/4I_2R_2$‡ | 18 | 0 |
| $(SIRP)_3$§ | 18 | 1 |
| $2SIRP/4I_2R_2$‡ | 24 | 2 |
| $2IRP/4I_2R_2$‡ | 24 | 4 |

I=isoniazid, P=pyrazinamide, R=rifampin, S=streptomycin sulfate

*Adapted from Snider and co-workers [19]
†Number in front of regimen indicates number of months—that is, 2 months initial phase/4 months continuation phase.
‡Continuation phase given twice a week.
§All drugs given 3 times a week for 6 months.

In addition to the ability of intensive drug regimens to reduce the duration of therapy to six months, these regimens offer new options for the initial management of tuberculosis where drug resistance is highly suggested—such as in patients from areas of Southeast Asia—or known to be present on the basis of past sensitivity testing, and for the management of patients for whom active tuberculosis is suggested strongly on clinical grounds but for whom all initial culture results are negative.

Table 4 summarizes current experience with various short-course treatment regimens for the management of patients with tubercle bacilli resistant to isoniazid or streptomycin therapy, or both. Regimens containing four or five drugs, at least one of which is rifampin, result in relapse rates of about 8% for patients with organisms resistant to isoniazid, streptomycin or both versus about 4.2% for patients with drug-sensitive organisms. The lower part of the table provides data that indicate that the differences in the sterilizing capacities of pyrazinamide and ethambutol that have been referred to previously carry over as well to situations that involve drug resistance. These data also point out that omitting rifampin in the continuation phase of therapy results in higher rates of relapse in the management of drug-resistant tuberculosis. When resistance to rifampin is present, the outcomes are not nearly as favorable, and therapy would need to be guided more specifically by the results of sensitivity

testing. Fortunately, resistance to rifampin is still relatively uncommon,[17] and, thus, for practical purposes, any of the rifampin-containing intensive regimens listed in Table 3 could be selected for therapy when drug resistance is suspected, even in the absence of confirmation by formal sensitivity test results.

When there is a strong suggestion clinically that a patient has active tuberculosis, but the diagnosis is not accompanied by positive cultures, the intensive drug regimens offer the prospect of very short durations of therapy that have high probabilities of cure. Three months of therapy with streptomycin, isoniazid, rifampin and pyrazinamide provide a greater than 90% probability of curing a patient who has active pulmonary tuberculosis when initial cultures are negative (Table 5).[21] Although this rate of cure is not as high as that achieved with a full six or nine months of therapy (Table 3), the use of three months of intensive therapy does provide a reasonable alternative to a longer course of therapy when the diagnosis of tuberculosis remains unconfirmed by culture.

TABLE 4.—*Relapse (%) After Short-Course Regimens of at Least 6 Months' Duration**

| Regimen | Drug-Sensitive Organisms | Drug-Resistant Organisms |
|---|---|---|
| IR, SIR | 3.6 to 7.3 | 12.0 to 14.0 |
| 4 or 5 drugs with R | 4.2 | 8.0 |
| 2SIRP/$S_2I_2P_2$†‡ | 5.2 | 11.0 |
| 2SIRE/$S_2I_2E_2$† | 16.1 | 36.0 |

E=ethambutol hydrochloride, I=isoniazid, P=pyrazinamide, R=rifampin, S=streptomycin sulfate

*Adapted from Mitchison and Nunn.[16]

†2 months initial phase/4 months (or more) continuation phase, with drug regimen in continuation phase given twice a week.

‡Some data derived from regimen given for 8 months.

TABLE 5.—*Results of Therapy for Culture-Negative Pulmonary Tuberculosis**

| Regimen | Subjects, Number | Relapse or Disease Months After Therapy 1-12 | 13-24 | >24 | Total Relapse |
|---|---|---|---|---|---|
| Selective chemotherapy† | 173 | 43 | 9 | 5 | 57 |
| 2SIRP‡ | 161 | 1 | 5 | 4 | 11 |
| 3SIRP‡ | 161 | 1 | 3 | 3 | 7 |
| 3SI(PA)/$6S_2I_2$‡§ | 160 | 0 | 0.6 | 1.2 | 2 |

I=isoniazid, P=pyrazinamide, (PA)=*para*-aminosalicylic acid, R=rifampin, S=streptomycin sulfate

*Adapted from Hong Kong Chest Service.[21]

†Antituberculosis therapy not started until active tuberculosis confirmed by positive culture, radiographic evidence or clinical deterioration; 72% (71/99) of cases of disease in this group subsequently had positive cultures; 48% (15/31) of failures in other groups subsequently had positive cultures.

‡Number in front of regimen indicates number of months.

§Initial phase of regimen/continuation phase; subscripts refer to times per week. This regimen constituted the standard control treatment regimen for this study.

Such therapy also is a better alternative to simply clinically observing such patients because more than 50% of them can be expected to have clinical progression of disease over a 60-month period (Table 5).[21]

In summary, current concepts that have integrated the knowledge gained from experimental models of tuberculosis and the treatment of human tuberculosis provide physicians with new options for short-term therapy that, for practical purposes, have all but ended the need for routine therapy that extends beyond nine months for virtually all types of clinical tuberculosis.[22]

## REFERENCES


1. Grosset J: Bacteriologic basis of short-course chemotherapy for tuberculosis, *In* Stead WW, Dutt AK (Eds): Tuberculosis. Clin Chest Med 1980; 1:231-241

2. David HL: Probability distribution of drug-resistant mutants in unselected populations of Mycobacterium tuberculosis. Appl Environ Microbiol 1970; 20:810-814

3. Dutt AK, Stead WW: Present chemotherapy for tuberculosis. J Infect Dis 1982; 146:698-704

4. Canetti G: Present aspects of bacterial resistance in tuberculosis. Am Rev Respir Dis 1965; 92:687-703

5. McCune RM, Tompsett R, McDermott W: The fate of Mycobacterium tuberculosis in mouse tissues as determined by the microbial enumeration technique—II. The conversion of tuberculous infection to the latent state by the administration of pyrazinamide and a companion drug. J Exp Med 1956; 104:763-802

6. Fox W, Mitchison D: Short-course chemotherapy for pulmonary tuberculosis. Am Rev Respir Dis 1975; 111:325-353

7. Mitchison DA: The action of antituberculosis drugs in short-course chemotherapy. Tubercle 1985; 66:219-225

8. McDermott W, Tompsett R: Activation of pyrazinamide in acidic environments in vitro. Am Rev Tuberc 1954; 70:748-754

9. Mackaness GB: The intracellular activation of pyrazinamide and nicotinamide. Am Rev Tuberc 1956; 74:718-728

10. Mitchison DA: Basic mechanisms of chemotherapy. Chest 1979; 79(suppl): 771s-781s

11. Dickinson JM, Mitchison DA: Bactericidal activity in vitro and in the guinea-pig of isoniazid, rifampicin and ethambutol. Tubercle 1976; 57:251-258

12. Jindani A, Aber VR, Edwards EA, et al: The early bactericidal activity of drugs in patients with pulmonary tuberculosis. Am Rev Respir Dis 1980; 121:939-949

13. Dickinson JM, Mitchison DA: Experimental models to explain the high sterilizing activity of rifampin in the chemotherapy of tuberculosis. Am Rev Respir Dis 1981; 123:367-371

14. Fox W: The chemotherapy of pulmonary tuberculosis: A review. Chest 1979; 76(suppl):s785-796

15. Mitchison DA: Treatment of tuberculosis—The Mitchell lecture 1979. J R Coll Physicians Lond 1980; 14:91-95, 98-99

16. Mitchison DA, Nunn AJ: Influence of initial drug resistance on the response to short-course chemotherapy of pulmonary tuberculosis. Am Rev Respir Dis 1986; 133:423-430

17. Grosset J: The sterilizing value of rifampin and pyrazinamide in experimental short-course chemotherapy. Tubercle 1978; 59:287-297

18. Hong Kong Chest Service/BMRC: Controlled trial of four thrice-weekly regimens and a daily regimen all given for 6 months for pulmonary tuberculosis. Lancet 1981; 1:171-174

19. Snider DE, Cohn DL, Davidson PT, et al: Standard therapy for tuberculosis 1985. Chest 1985; 87(suppl):117s-124s

20. Dutt AK, Moers D, Stead WW: Undesirable side effects of isoniazid and rifampin in largely twice-weekly short-course chemotherapy for tuberculosis. Am Rev Respir Dis 1983; 128:419-424

21. Hong Kong Chest Service: Controlled trial of 2-month, 3-month, and 12-month regimens of chemotherapy for sputum-smear-negative pulmonary tuberculosis. Am Rev Respir Dis 1984; 130:23-28

22. Dutt AK, Moers D, Stead WW: Short-course chemotherapy for extrapulmonary tuberculosis—Nine years' experience. Ann Intern Med 1986; 104:7-12

Epitomes

Important Advances in Clinical Medicine

# Orthopedics

*The Scientific Board of the California Medical Association presents the following inventory of items of progress in orthopedics. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, research workers or scholars to stay abreast of these items of progress in orthopedics that have recently achieved a substantial degree of authoritative acceptance, whether in their own field of special interest or another.*

*The items of progress listed below were selected by the Advisory Panel to the Section on Orthopedics of the California Medical Association and the summaries were prepared under its direction.*

Reprint requests to Division of Scientific and Educational Activities, California Medical Association, PO Box 7690, San Francisco, CA 94120-7690

## Shoulder Arthroscopy

ARTHROSCOPIC STUDIES of the shoulder joint have significantly increased our knowledge of the anatomy and pathologic disorders of the shoulder joint, emphasizing the complex nature of the shoulder function. The shoulder joint is commonly a source of pain, and diagnostic modalities that accurately evaluate the soft tissue source of pain have traditionally been limited. Arthroscopy has allowed direct visualization and identification of shoulder disorders heretofore not understood and has further clarified the interrelationships and evolution of pathologic conditions of the shoulder joint.

The indications for shoulder arthroscopy include pain, clicking or catching within the shoulder joint that interferes with function and is not otherwise identified by clinical tests. Loose bodies detected radiographically can be removed, a shoulder joint with degenerative disease can be debrided, septic joints can be drained, synovectomy can be done in cases of chronic synovitis, articular surface problems can be evaluated and biceps tendon lesions can be identified.

Isolated glenoid labral tears, previously poorly understood, have become associated with clinical syndromes and may be treated by simple arthroscopic resection of the torn area.

Shoulder instability has been further evaluated to identify a spectrum of clinical instability, with arthroscopic surgical techniques being applied for both diagnosis and treatment of shoulder instability, including the stabilization and evaluation of acute shoulder dislocations. Arthroscopic stabilization of an unstable shoulder by percutaneous techniques that fix the anterior capsule to the glenoid neck have been developed.

Arthroscopic evaluation of the rotator cuff and subdeltoid bursa has allowed the evolution of surgical techniques that decompress the coracoacromial arch by resecting the coracoacromial ligament and removing bone from the inferior surface of the acromion to treat the classic impingement syndrome. Other rotator cuff syndromes, including partial rotator cuff tear associated with pain on throwing, have been identified and treated by simple arthroscopic debridement.

A precise surgical technique coupled with experience in developing the technical skills of shoulder arthroscopy is required to keep complications to a minimum. Shoulder arthroscopy is an effective adjunct for identifying and managing shoulder disorders and to further understand the spectrum of shoulder disease.

WESLEY M. NOTTAGE, MD
*Laguna Hills, California*

### REFERENCES

Andrews JR, Carson WG Jr, Ortega K: Arthroscopy of the shoulder: Technique and normal anatomy. Am J Sports Med 1984; 12:1-7

Johnson LL: Arthroscopic Surgery Principles and Practice, 3rd Ed. St Louis, CV Mosby, 1986, pp 1301-1445

Pappas AM, Goss TP, Kleinman PK: Symptomatic shoulder instability due to lesions of the glenoid labrum. Am J Sports Med 1983; 11:279-288

## Microvascular Transfer of Bone—An Update

MICROVASCULAR RECONSTRUCTIVE OPERATIONS offer new therapeutic solutions for difficult bone loss problems. Various bones are used for vascularized bone grafts including rib, scapula, iliac crest, radius and fibula. The two bones most commonly used for vascularized grafts are the fibula and iliac crest. Donor selection is based on the length and shape of the defect and the need for additional tissues such as skin, fat and muscle at the recipient site.

For a long-bone defect greater than 6 cm, vascularized bone grafts have been shown to heal faster and with greater union rate than nonvascularized grafts. These large defects commonly occur following limb-salvage procedures for both malignant and locally aggressive bone tumors and in patients with chronic osteomyelitis or traumatic bone loss. Other indications include congenital pseudarthrosis of the tibia.

Long-bone defects are most commonly treated with fibular grafts that are transferred with their vascular supply formed by the peroneal artery and vein. Advantages of the fibula as donor include a length of up to 30 cm and the ability to include muscle and overlying skin if needed. For smaller defects or those conditions requiring anatomic sculpturing of the donor bone, the iliac crest is an excellent choice. The iliac crest with a groin flap is especially useful when there is bone loss accompanied by extensive soft tissue loss. The vascular pedicle is formed by the deep circumflex iliac artery and vein.

Results of these procedures are best in patients who un-

dergo limb reconstruction after resection of a bone tumor (87% primary union rate) and for forearm or mandibular defects (100% primary union rate). For the most difficult cases of chronic osteomyelitis, 60% of vascularized grafts ultimately heal.

Vascularized bone grafts have the advantage of maintaining a physiologic blood supply, thus not depending on subsequent revascularization; preserving live osteocytes, osteoblasts and osteoclasts, and greater bone strength. Contraindications to microvascular transfer of bone include a patient who is a poor risk for a lengthy operative procedure, a limb with limited salvage potential and where there is a probability of success with a conventional bone graft.

GARY K. FRYKMAN, MD
*Loma Linda, California*

#### REFERENCES

Moore JR, Weiland AJ: Free vascularized bone and muscle flaps for osteomyelitis. Orthopedics 1986 Jun; 9:819-824

Weiland AJ, Moore JR, Daniel RK: Vascularized bone autografts—Experience with 41 cases. Clin Orthop 1983 Apr; 174:87-95

Wood MB: Free vascularized bone transfers for nonunions, segmental gaps, and following tumor resection. Orthopedics 1986 Jun; 9:810-816

Wood MB, Cooney WP III, Irons GB Jr: Skeletal reconstruction by vascularized bone transfer: Indications and results. Mayo Clin Proc 1985 Nov; 60:729-734

## Immediate Stabilization of Fractures in Patients With Multiple-Systems Injuries

SEVERE HEAD INJURY and uncontrolled hemorrhage remain the primary causes of early death in victims of multiple-systems trauma. If a victim survives the first 24 to 48 hours, the most common cause of death is adult respiratory distress syndrome (ARDS), followed by multiple-systems organ failure and sepsis.

Traditionally, treatment of fractures has been relegated to the lowest priority during the initial treatment phase. Recent evidence suggests, however, that immediate stabilization of unstable fractures of the femur, pelvis and occasionally the spine may play a major role in reducing the morbidity and mortality in these patients. Immediate stabilization of other long bone fractures, such as the humerus, may be indicated as well.

Immediate stabilization of fractures offers many advantages in patients with multiple-systems injuries: Stabilization of fractures significantly reduces pain, which reduces the need for narcotics. Narcotics are respiratory and cerebral depressants, and their use increases the need for ventilatory support and possibly the incidence of ARDS. Fracture stability facilitates nursing care and increases patient mobility, permitting a vertical chest position essential for pulmonary care. Greater patient mobility also lowers the incidence of decubitus ulcers, thrombophlebitis and other phenomena associated with prolonged bed rest. Immediate fracture stability allows joints and muscles to be rehabilitated earlier, resulting in an earlier return to function and a better long-term result from musculoskeletal injuries. A group of patients with immediate stabilization of major fractures was compared with a historical control in which early fracture stabilization was not done. When the injury severity score was between 26 and 40, early fracture stabilization reduced the incidence of ARDS from 32% to 9%, mortality dropped from 9.3% to 3.4% and length of hospital stay was cut by 50%. Others have shown similar outcomes.

Immediate stabilization of fractures in these polytrauma patients can be challenging, as the fractures are often complex and open. One or more surgical teams experienced in the treatment of patients with multiple injuries are usually necessary to achieve immediate stabilization of major fractures without undue morbidity.

M. W. CHAPMAN, MD
*Sacramento, California*

#### REFERENCES

Hanscom DA, Chapman MW, Holcroft J: Immediate Fixation of Fractures in Patients With Multiple System Trauma. Presented to the American Academy of Orthopaedic Surgeons Annual Meeting, New Orleans, February 1986

Johnson KD, Cadambi A, Seibert GB: Incidence of adult respiratory distress syndrome in patients with multiple musculoskeletal injuries: Effect of early operative stabilization of fractures. J Trauma 1985 May; 25:375-384

Lozman J, Deno DC, Feustel PJ, et al: Pulmonary and cardiovascular consequences of immediate fixation or conservative management of long-bone fractures. Arch Surg 1986 Sep; 121:992-999

Riska EB, von Bonsdorff H, Hakkinen S, et al: Prevention of fat embolism by early internal fixation of fracture in patients with multiple injuries. Injury 1976 Nov; 8:110-116

Riska EB, von Bonsdorff H, Hakkinen S, et al: Primary operative fixation of long bone fractures in patients with multiple injuries. J Trauma 1977 Feb; 17:111-121

## Recent Advances in the Treatment of Chronic Posttraumatic Osteomyelitis of the Tibia

THE PERSISTENCE of bone infection can be attributed to the presence of sequestrum, nonunion of a fracture or retained metal used for internal fixation. Control of bone infection requires debriding all sequestra and surrounding necrotic tissue with the administration of appropriate antimicrobial therapy. In ununited tibial fractures, bone debridement followed by cancellous bone-grafting procedures and external fixation have achieved a high rate of bony union. Following healing of the fracture, infection is more easily managed and in many instances eradicated.

Optimal treatment of chronic osteomyelitis of the tibia is often adversely affected by the absence of an adequate soft tissue envelope. The use of local muscle flaps to reestablish adequate soft tissue coverage improves infection control. In addition, recent advances in microvascular techniques have allowed for the transfer of muscle, myocutaneous, osseous and osteocutaneous flaps to the tissue-deficient site. In our experience, the use of local muscle flaps or vascularized free-tissue transfers, in combination with appropriate orthopedic procedures and antimicrobial therapy, has resulted in an increased success rate in the treatment of this difficult problem.

M. J. PATZAKIS, MD
J. WILKINS, MD
R. SHERMAN, MD
*Los Angeles*

#### REFERENCES

Fitzgerald RH Jr, Ruttle PE, Arnold PG, et al: Local muscle flaps in the treatment of chronic osteomyelitis. J Bone Joint Surg [Am] 1985; 67:175-185

Patzakis MJ, Watkins R, Harvey JP Jr: Postero-lateral Bone Grafting for Infected Non-unions of the Tibia, *In* Moore TM (Ed): American Academy of Orthopaedic Surgeons Symposium on Trauma to the Leg and Its Sequelae. St Louis, CV Mosby, 1981, pp 235-240

Weiland AJ, Moore JR, Daniel RK: The efficacy of free tissue transfer in the treatment of osteomyelitis. J Bone Joint Surg [Am] 1984 Feb; 66:181-193

## Biopsy of Primary Bone Tumors

IN THIS ERA of limb salvage, the "simple" biopsy is a crucial determinant of patient outcome. Precautions relate to the timing of biopsy, the type of biopsy, the direction of incisions, arthroscopic biopsy, the extent of a biopsy and the use and placement of wound suction.

Biopsy trauma alone may increase the apparent tumor extent as seen on imaging studies. Therefore, all local staging procedures—that is, isotope scans, angiograms, computed tomography and magnetic resonance imaging—should be done before the biopsy. An open biopsy is usually best.

Closed biopsy may be useful to diagnose suspected metastases to bone, but histologic diagnosis of primary tumors can be difficult, requiring larger tissue specimens for multiple studies including special stains, immunoperoxidase studies and electron-microscopic evaluation. Frozen section confirmation that representative tissue has been obtained is always advisable. Alignment of biopsy incisions is crucial because the scar must later be resected en bloc with the tumor. Incisions should be vertical on the extremities and transverse only at the pelvic rim and joint flexion creases. Poorly placed incisions can prevent any attempt at preserving a limb and can force amputation. It is suggested that a preliminary biopsy be done only by a physician who is fully qualified to carry out the definitive surgical procedure. Arthroscopic biopsy in the evaluation of joint symptoms due to an adjacent tumor is contraindicated. Transsynovial biopsy of a tumor will seed the entire joint with cells, creating an exceptionally difficult surgical problem.

For a number of reasons, only a peripheral wedge of tumor should be excised to show its type and highest cellular grade. Peripheral tissue is often less mineralized and easier to cut for frozen section. Bleeding is easier to control after a peripheral biopsy than a larger, deeper incision, and further weakening of the bone is avoided. Management of the biopsy site should include rigorous hemostasis and wound suction to help prevent dissemination of tumor cells along adjacent fascial planes. Suction tube(s) are brought out in line with the incision to facilitate later en bloc resection.

TILLMAN MOORE, MD
*Los Angeles*

#### REFERENCES

Enneking WF: The issue of the biopsy (Editorial). J Bone Joint Surg [Am] 1982 Oct; 64:1119-1120

Joyce MJ, Mankin HJ: Caveat arthroscopos: Extra-articular lesions of bone simulating intra-articular pathology of the knee. J Bone Joint Surg [Am] 1983 Mar; 65:289-292

Mankin HJ, Lange TA, Spanier SS: The hazards of biopsy in patients with malignant primary bone and soft-tissue tumors. J Bone Joint Surg [Am] 1982 Oct; 64:1121-1127

Moore TM: Closed biopsy, *In* Harrington K (Ed): Orthopaedic Management of Metastatic Bone Disease. St Louis, CV Mosby, 1987, in press

Simon MA: Biopsy of musculoskeletal tumors. J Bone Joint Surg [Am] 1982 Oct; 64:1253

## Alternatives to Cemented Joint Prostheses

ALTHOUGH THE CEMENTED total hip replacement has outperformed all other reconstructive procedures for the arthritic hip, ten-year follow-up studies have shown a loosening rate at the bone-cement junction approximating 25%. Additionally, osteolysis, in some part due to the fragmentation of cement and the body's response to this particulate debris, may make further reconstruction difficult. The cementless total hip replacement has been developed to overcome this long-term loosening and osteolysis.

Cementless technology has developed along two conceptual lines. The Europeans have concentrated their efforts on macrointerlock of bone to prosthesis, while North Americans have concentrated on microinterlock of bone to prosthesis. Macrointerlock prostheses, because of their mechanical weakness, relatively high loosening rate and difficulty in removal due to bony ingrowth, have few proponents in this country.

The microinterlock prosthesis is now used rather extensively in this country, especially in the treatment of arthritic problems in younger patients. In the microinterlock system, the prosthesis is coated with beads or wires, creating 200 to 500 micron surface pores on the prosthetic surface for bony ingrowth. Several problems inherent in this technique must be recognized. The process of attaching the porous material to the prosthesis significantly weakens its structure and may cause it to break in the long term. The percentage of pores that actually are ingrown with bone varies substantially in studies, but it appears that only about 30% of the material is actually ingrown with bone. Thus, the question remains whether these devices will actually biologically bond with the femur and the acetabulum. Other problems include low-grade pain and limp, technical difficulty in implanting the prosthesis and stress shielding or resorption of unstressed bone. Despite these cautions, excellent short-term results have been reported.

It is important to continue to develop new concepts and techniques of biologic bonding of prosthesis to bone. Cement has certainly been effective, but osteolysis is of significant concern. Microinterlock shows promise in the short term. What long-term problems it will engender are yet to be seen.

RICHARD B. WELCH, MD
*San Francisco*

#### REFERENCES

Amstutz HC: Arthroplasty of the hip: The search for durable component fixation. Clin Orthop 1985 Nov; 200:343-361

Engh CA, Bobbyn JD, Mathews JG II, et al: Biologic fixation of a modified moore prosthesis, *In* The Hip Society: Proceedings of the Twelfth Open Scientific Meeting of the Hip Society. St Louis, CV Mosby, 1984, pp 95-131

## Orthopedic and Soft Tissue Applications of Magnetic Resonance Imaging

MAGNETIC RESONANCE IMAGING (MRI) is a relatively new noninvasive diagnostic technique that uses magnetic fields and radio-frequency signals to generate cross-sectional representations of internal anatomy. Advantages of the technique include the absence of a known biologic hazard, direct multiplanar imaging capability without sacrifice of spatial resolution and the ability to provide excellent discrimination among various normal and pathologic soft tissue structures. MRI has been shown to provide useful diagnostic insight into various orthopedic disorders, particularly those affecting muscles, tendons, ligaments, articular cartilage and bone marrow.

The method shows greater sensitivity than skeletal scintigraphy in the early diagnosis of ischemic necrosis involving the femoral head and has shown promising preliminary results in the evaluation of this disease at other sites. Owing to its extreme sensitivity for pathologic processes that begin in bone marrow, MRI can also contribute to the early diagnosis of acute hematogenous osteomyelitis, metastatic disease to the skeleton and myeloproliferative disorders. In the staging of primary osseous neoplasms, the technique is superior to computed tomography (CT) in determining the degree of marrow involvement and soft tissue extension, although cortical bone destruction and matrix calcification or ossification are slightly less well depicted.

MRI has contrast discriminating capabilities that offer advantages over CT, particularly in establishing the precise extent of primary soft tissue pathology, including infection and neoplastic disease. In cases of severe trauma, especially those involving the knee joint, the method can reliably diagnose meniscal damage, cruciate and collateral ligament tears, articular cartilage pathology and intra-articular effusion. MRI may eventually replace arthrography and CT in the evaluation of internal derangements affecting the temporomandibular

joint. As clinical experience is gained and technical improvements are made, the technique should also become important in the initial assessment of synovial inflammatory disorders.

In the spine, MRI offers accuracy comparable to that of CT and myelography in the diagnosis of intervertebral disc herniation and is more sensitive to early disc degeneration. In addition, the method can assist in the early diagnosis and characterization of disc space infections and may be beneficial in the follow-up of patients who have undergone a spinal operation or chemonucleolysis.

Patients with total joint replacements and other orthopedic hardware can be safely evaluated by MRI, and image degradation by artifacts is less of a problem than with CT. The technique has also been successfully applied to diverse orthopedic conditions, including the carpal tunnel syndrome, Legg-Calvé-Perthes disease, rotator cuff tear and other glenohumeral joint disorders, stress fractures and pedal neuromas. The potential of MRI as applied to orthopedic disease is yet to be fully explored, and spectroscopy of phosphorus 31 as well as other nuclei may yield valuable insight into the physiologic aspects of such disorders in the future.

DAVID J. SARTORIS, MD
DONALD RESNICK, MD
*San Diego*

REFERENCES

Berquist TH, Ehman RL, Richardson ML (Eds): Magnetic Resonance of the Musculoskeletal System. New York, Raven Press, 1987

Pettersson H, Hamlin DJ, Mancuso A, et al: Magnetic resonance Imaging of the musculoskeletal system. Acta Radiol 1985 May-Jun; 26:225-234

Richardson ML (Ed): Magnetic resonance Imaging of the musculoskeletal system. Radiol Clin North Am 1986 Jun; 24:135-335

## Meniscal Repair

A SYMPTOMATIC meniscal tear, especially in the young, is a serious injury with potentially grave consequences for the knee because the menisci enhance joint stability and reduce the compressive forces sustained per unit area of articular cartilage.

The therapeutic approach to meniscal tears depends on the tear type, location, associated ligamentous injuries and the age and activity of the patient. Treatment options include meniscectomy, partial meniscectomy and meniscal repair. Total meniscectomy is rarely necessary and is not to be undertaken lightly as degenerative arthritis may result. Arthroscopic partial meniscectomy spares portions of the meniscus, allowing for partial fulfillment of its weight-bearing and joint stabilization roles. Although degenerative changes are less likely to develop, joint mechanics are still altered. Meniscal repair, if feasible, preserves normal knee mechanics and logically should provide superior long-term results.

Certain meniscal tears should and do heal. The outer (peripheral) 25% of the meniscus has been shown to be vascular, and healing originates from the peripheral synovial tissues. Meniscal repair can be achieved by open (arthrotomy) and closed (arthroscopy) methods. The arthroscopic method affords greater access to the posterior horn of the lateral meniscus, tears slightly within the meniscocapsular junction and tears deep to the collateral ligaments.

Arthroscopic meniscal repair involves four steps: selecting appropriate tears, preparing the tear margins and adjacent synovium, suturing the tear and rehabilitating postoperatively. Meniscal tears amenable to repair are longitudinal tears more than 1.5 cm within the vascular zone, without serious secondary tears and with demonstrable hypermobility. In addition, ligamentous stability is required. In our experience, 15% of all meniscal tears are repairable.

THOMAS D. ROSENBERG, MD
LONNIE E. PAULOS, MD
RICHARD D. PARKER, MD
*Salt Lake City*

REFERENCES

Rosenberg TD, Scott SM, Coward DB, et al: Arthroscopic meniscal repair evaluated with repeat arthroscopy. Arthroscopy 1986; 2:14-20

Rosenberg TD, Scott SM, Paulos LE: Arthroscopic surgery: Repair of peripheral detachment of the meniscus. Contemp Orthop 1985 Mar; 10:43-50

## Sports Footwear

SIGNIFICANT ADVANCES have occurred in the design and manufacture of sports footwear. The use of impact-absorbing synthetic plastics such as polyurethane and ethylene vinyl acetate has resulted in lighter weight shoes that are resilient and durable yet flexible.

Scientific studies of the mechanisms of sports injuries have found an association with footwear in certain instances. In football, severe knee and ankle injuries can be caused by unyielding foot fixation. This had led to the widespread use of soccer style shoes with molded rubber cleats that develop less torque at the shoe-surface interface than traditional shoes.

Knowledge of the foot and ankle stresses sustained in different activities has stimulated the production of "sports specific" shoes. Shoes specifically designed for running, aerobics and court sports are not interchangeable. For example, running shoes provide hindfoot cushioning and stabilization to withstand loads of as much as three times body weight at heel strike. This is achieved by a thickened sole, a flared heel and a firm, snugly fitting counter. Significant plantar flexion has been shown to decrease cyclic loading of the Achilles tendon.

Court shoes used for tennis and racquetball must accommodate pivoting and lateral movements. Low-profile rubber soles provide increased traction but do not afford the same shock-absorbing capacity as running shoes. In addition, minimal heel elevation that facilitates quick and explosive movements does not relax the Achilles tendon.

The most important criteria in shoe selection are fit and comfort. The longest toe should clear the end of the toe box by half an inch. Leather uppers are generally more expensive but conform best to the shape of the foot over time, thus increasing comfort.

With the exception of barefooted placekickers and occasional runners, the effect of recent developments in footwear has been to maximize performance while decreasing the risk of injury.

RICHARD A. MARDER, MD
*Sacramento, California*

REFERENCES

Cavanagh PR: The Running Shoe Book. Mountain View, Calif, World Publications, 1981

Stamford B: Choosing shoes for your sport. Physician Sportsmed 1984 Oct; 12:191

## Osseous and Osteochondral Allografts

BONE AND CARTILAGE allografts have proved to be feasible and practical alternatives for reconstructing arthritic joints, obliterating bone defects following trauma or bone dissolution due to various causes and replacing large segments of bone destroyed by bone tumors. The use of allografts to replace large bone defects in revisions for failed total hip replacement has been successful. The allograft bridges the bone defect and provides a scaffold for the ingrowth of vascularized connective tissue that carries the elements necessary for new bone

production. The latter occurs by resorption and replacement of dead trabeculae and appositional growth around dead trabeculae.

Although there is an immune response to transplanted allograft bone, immunosuppressive drugs are not used to neutralize the reaction because of their serious side effects. Graft immunogenicity may be reduced by freezing the allograft before transplantation and forcefully lavaging the allograft bone to remove the fat cells and hematopoietic elements that provoke an immune response in a patient.

Treatment of cartilage allografts with dimethyl sulfoxide and 10% glycerine before freezing has been reported to maintain viability of about 50% of donor chondrocytes. There is a question, however, as to the capacity of these cells to produce collagen and mucopolysaccharides after thawing and transplantation.

More recently there have been reports of the successful resurfacing of portions of synovial joints in the lower extremities with fresh nonfrozen composite graft of hyaline cartilage and bone. The bone portion provokes a clinically insignificant immune response. The cartilage of the graft is thought to be "immunologically privileged" because the matrix prevents the diffusion of large molecules of antigens and antibodies. Because of this, the afferent and efferent arms of the immune reaction cannot interact and produce a rejection response.

MARVIN H. MEYERS, MD
*La Jolla, California*

#### REFERENCES

Gross AE, Silverstein EA, Folk J, et al: The allotransplantation of partial joints in the treatment of osteoarthritis of the knee. Clin Orthop 1975; 108:7-14

Harris WH, Crothers O, Oh I: Total hip replacement and femoral-head bone-grafting for severe acetabular deficiency in adults. J Bone Joint Surg [Am] 1977 Sep; 59:752-759

Meyers MH: Resurfacing of the femoral head with fresh osteochondral allografts. Clin Orthop 1985 Jul-Aug; 197:111-114

Parrish FF: Treatment of bone tumors by total excision and replacement with massive autologous and homologous grafts. J Bone Joint Surg [Am] 1973; 55:1-22

## Endoprosthetic Limb Salvage Operation for Malignant Bone Tumors

THE HISTORICAL APPROACH to the local control of primary malignant bone tumors, including osteosarcoma, chondrosarcoma, fibrosarcoma, malignant fibrohistiocytoma and, in certain instances, Ewing's sarcoma, has been amputation. Recent advances in surgical resection techniques, muscle transfers and improved mechanical design of custom endoprostheses have established the limb-sparing operation as a possible alternative for local control of malignant bone tumors when coupled with preoperative adjuvant therapy.

Two basic goals must be achieved by a limb-sparing operation for malignant bone tumors. The local recurrence rate in a salvaged extremity should be no higher than that achieved with amputation, and the reconstructed extremity should be enduring and functional, without requiring repetitive hospital admissions for the management of local complications or complex revisional procedures.

The functional results of endoprosthetic reconstruction following wide resection for malignant bone tumors have been excellent about the knee and good to excellent at the hip. Scapular and proximal humeral replacements permit normal hand and elbow function and avoid the need for orthoses and cumbersome prostheses. For pelvic lesions, an internal hemipelviectomy, when feasible, retains the extremity and results in an extremity with good cosmetic appearance and moderate function. Neurovascular gastrocnemius muscle transfers permit endoprosthetic replacement of the proximal tibia with the anticipation of reasonable extensor function of the knee. Expandable prostheses make limb salvage for a very young patient, especially with Ewing's sarcoma, feasible.

Preoperative chemotherapy and radiation therapy have decreased the local recurrence rate after a limb-sparing operation to 5%, not statistically different from the local recurrence rates seen following amputation. In the absence of preoperative adjuvant chemotherapy, the reported local recurrence rates range between 20% and 60%.

In summary, limb-sparing surgical techniques using improved custom endoprostheses with preoperative adjuvant chemotherapy now permit a limb-sparing operation in most patients presenting with primary malignant bone tumors. Amputation for the primary control of malignant bone tumors continues to be indicated for those patients who present with very large tumors, those with incorrectly placed or infected biopsy incisions and patients who present with tumors of the distal tibia or the foot.

JEFFREY J. ECKARDT, MD
*Los Angeles*

#### REFERENCES

Eckardt JJ, Eilber FR, Dorey FJ, et al: The UCLA experience in limb salvage surgery for malignant tumors. Orthopedics 1985; 8:612-621

Eilber FR, Eckardt JJ, Morton DL: Advances in the treatment of sarcomas of the extremity: Current status of limb salvage. Cancer 1985 Dec; 54:2695-2701

ADVISORY PANEL TO THE SECTION ON ORTHOPEDICS

MICHAEL W. ABDALLA, MD
*Advisory Panel Chair*
*CMA Scientific Board Representative*
*Orange*

PRESTON M. JAMES, MD
*CMA Section Chair*
*San Francisco*

WILLIAM TIPTON, JR, MD
*CMA Section Secretary*
*Sacramento*

BLAIR C. FILLER, MD
*CMA Section Assistant Secretary*
*Inglewood*

GEORGE WIESSEMAN, MD
*Loma Linda University*

DAVID S. SCHURMAN, MD
*Stanford University*

ROBERT SZABO, MD
*University of California, Davis*

ROBERT A. BAIRD, MD
*Section Editor*
*University of California, Irvine*

GERALD FINERMAN, MD
*University of California, Los Angeles*

WAYNE H. AKESON, MD
*University of California, San Diego*

JAMES H. MORRIS, MD
*University of California, San Francisco*

TILLMAN MOORE, MD
*University of Southern California*

RICHARD B. WELCH, MD
*San Francisco*

## Health Care in a Dreamworld

THE REMARKABLE ACHIEVEMENTS of medical science and technology, and the social, economic and political responses to these achievements have produced a kind of dreamworld in health care. Depending upon one's point of view, the dreams may be good or bad. In any case, it is not nature's way to dream forever. It is reasonable to expect that someday there will be an awakening and it will be discovered that the dreams were never real, and that reality is something different.

The dreams are many. Some are the dreams of society as a whole, some are of health planners wherever they may be and some are of physicians, other health professionals or the medical profession itself. Most are all too familiar:

- A free market and profit incentives in health care will, over time, solve the problems of health care distribution and will lower costs.
- Competition will provide a better product at lower cost, as it has done in so many other aspects of American life.
- The excess numbers of physicians and other health care providers will meet, or more than meet, the needs for health care services in medically underserved areas.
- Medical science should, by now, achieve near perfection in health care or someone or something must be to blame.
- Medical science has now displaced the need to study and practice the traditional art in patient care.
- Prevention and health education will reduce health care costs because fewer people will get sick and everyone will live longer.

All these are fantasies, often heavily laced with wishful thinking. Yet it is beliefs such as these that seem to dominate a dreamworld of health care in which this nation now finds itself.

Then there are some really bad dreams. For some they may even seem like nightmares. Funding for the care of the poor, the disadvantaged and underprivileged is being more or less systematically reduced, with now measurable deterioration in the health status of many of them. Physicians are finding themselves no longer always in charge of patient care but nevertheless being held individually and collectively responsible for it in the minds of the public and in the courts of law. Medicare, Medicaid, DRGs, PROs, government regulations and the requirements of private sector payors in patient care all too often are producing costly administrative nightmares for physicians and hospitals and siphoning off dollars that might otherwise be used to provide needed care. And then there are conflicts among physicians and conflicts with hospital administrators and with other health professionals who may seek to occupy more and more of physicians' role and turf. The list of bad dreams, nightmares and potential nightmares could go on and on. As physicians know, the list these days is a long one.

But sooner or later there must come an awakening. It will never be profitable to provide care for those who cannot pay. There is accumulating evidence that the health of disadvantaged youth, particularly among the minorities, is worsening. The free market makes a travesty of anything like equity in health care. Medicine is not an exact science and never will be. It is also a fact that the longer more people live, the more health care they may be expected to consume, with the attendant greater costs. It is a reality that there will never be enough dollars to do everything we now know how to do for every patient. Yet at the same time dollars are being spent for frills, profit-making ventures and the like, rather than on genuinely needed health care. After all, health care is for people, not just for governments, corporations, investors or profiteers. Denied or deferred care is not likely to be cost effective for patients or for society.

What to do? Will this dreamworld go on forever? It is patently unrealistic and inefficient. As someone has said, health care has become a crazyquilt patchwork of ad hoc interventions, usually based on incorrect assumptions, that in general have created more problems than they have solved. As a result many of the solutions are now becoming the problems. Perhaps it is time to get back to some fundamentals such as,

- Recognize the important but actually limited role of medical science and technology in overall patient care.
- Study, define and perhaps even begin to measure what goes on in a clinical encounter between doctor and patient, and what it takes to give satisfaction to both.
- Address the social, economic and political issues that arise from medical progress, whether in individual patient care or elsewhere in the health care enterprise, and seek consensus among the interested parties about what to do and how to do it.

Conflicting interests abound in all of this, and in the real world of health care ways must be found to balance these various interests in what will always be dynamic and changing situations. In the meantime the dreams and the nightmares both run rampant in the professional and public consciousness, or perhaps one should say unconsciousness. In the meantime, much that is valuable in health care is being unnecessarily lost to patients and to society.

MSMW

## Diagnosis and Treatment of Smell and Taste Disorders

THE DIAGNOSIS AND TREATMENT of chemosensory disorders have recently received more attention than in the past several years. This increased interest has focused both on the development of improved diagnostic tests and on a deeper understanding of the physiological mechanisms involved in the chemical senses.

Quantification of olfactory (or gustatory) deficits has been limited by the fact that the precise types of measurement needed to diagnose a disorder are not well understood. The tests commonly used to diagnose a general smell or taste loss include threshold and identification tasks. For threshold measurements, one can determine the concentration at which a stimulus is first detected (a detection threshold) or first recognized and labeled (a recognition threshold). Quantification of detection thresholds is straightforward while determination of recognition thresholds is not. The recognition problem lies in the fact that we do not have a standardized vocabulary to assign to most odors and tastants. Thus, at low concentrations when an odor such as lemon is first recognized, it may be

labeled "fruity" by one subject, "floral" by another and "like menthol" by a third.

Odor (or taste) identification tests are used to determine a patient's ability to evaluate suprathreshold intensities. For example, a person is presented with common odors (which are mixtures of compounds) and asked to identify them from a list that contains the correct label for the odor along with several incorrect labels. Identification tasks and detection thresholds are appropriate tests in a physician's office for a rough diagnosis of general chemosensory loss. Both measurements have recently been used by Davidson and co-workers—described elsewhere in this issue—to quantify olfactory deficits and develop diagnostic categories. These experimenters arbitrarily assigned a value of 50 to a detection threshold test and 50 to the identification test. A perfect score was designated "100"; mildly hyposmic, 60 to 80; moderately hyposmic, 40 to 60; severely hyposmic, 20 to 40, and anosmic, 0 to 10. These scores along with rhinomanometry, nasal cytology, nasal endoscopy, computed tomographic scans and responses to medical treatment were used to develop seven diagnostic categories of olfactory dysfunction: inflammatory, postviral, trauma, toxins, congenital, psychiatric and miscellaneous. Similar categories have been proposed by others, including Schiffman[1] and Henkin.[2]

While a single score derived from detection and identification tasks can be used to diagnose global chemosensory decline, it may not pinpoint more selective deficits. A method of measurement called "magnitude estimation" that determines the relation between perceived intensity and concentration can sometimes be helpful in such cases.[3] When log concentration for a single compound is plotted on the abscissa and log perceived intensity on the ordinate, some compounds are found to have very flat functions while others rise more steeply. Flat functions indicate that large increases in concentration of a stimulus are necessary to achieve small increments in perceived intensity. Steep functions indicate that even small increases in concentration of a stimulus can lead to large increases in perceived intensity. Receptors for stimuli with flatter slopes presumably saturate more quickly than those with steeper slopes. This may result from the fact that there are only a few receptor sites for a given compound and these saturate quickly due to a much greater number of stimulus molecules relative to the number of receptors. If a patient is found to have significantly flatter slopes for a small selection of compounds relative to a control group while the slopes for the remainder of the stimuli are identical to controls, this suggests a selective loss in certain receptor types. This is frequently found in persons with exposure to toxic chemicals (S. Schiffman, PhD, unpublished data, May 1974 to February 1987). A threshold test does not pinpoint the problem as there are still enough receptors left to yield normal threshold values. Identification tests do not isolate the loss as the stimuli are generally mixtures and thus few items are labeled incorrectly.

Discrimination tasks are necessary to identify subtle losses in a patient's ability to distinguish between suprathreshold sensations. Three approaches are helpful. First, subjects may sniff three bottles, two of which contain the same odorant; they are asked to identify the bottle containing the different odorant. Second, a person may quantify the degree of similarity between two odors of a pair by marking a line labeled "identical" at one end and "completely different" at the other. Third, a series of odorants can be rated on adjective scales such as "fruity," "floral" or "unpleasant." The first two tests help identify losses in the ability to discriminate among various types of wines or coffees, for example. The third is sometimes useful in diagnosing dysosmia or dysgeusia (distortions in smell and taste).

The development of truly sophisticated tests, however, probably awaits a deeper understanding of transduction mechanisms in the chemical senses. In olfaction, it has been shown that adenylate cyclase is involved in mediating certain odors.[4] The phosphatidylinositol system may play a role for others.[5] Sodium channels[6] and adenosine receptors[7,8] are known to be involved in gustatory transduction. The appropriate selection of stimuli must cover the range of receptors and channels known to mediate smell and taste. Until more knowledge about these mechanisms is gained, we will probably not be able to fully understand and properly diagnose many chemosensory disorders, especially those that result from pharmacological agents, toxic compounds and metabolic disorders.

Not only diagnosis but better treatment strategies as well await further understanding of the biochemistry of olfaction and taste. Chemosensory losses will often require treatments that amplify the signal. While no practical means have yet been found to treat gustatory disorders, several means for potentiation are now known. 5′-Ribonucleotides have long been used as taste enhancers.[9] Salt taste has recently been shown to be slightly potentiated after topical application of the quaternary ammonium compound bretylium tosylate to the tongue.[10] Bretylium tosylate is an antifibrillary drug[11] that has been shown to increase sodium transport through amiloride-sensitive sodium channels in frog skin.[12,13] Caffeine and other methyl xanthines including theophylline and theobromine have been shown to enhance the taste of salt and some sweeteners.[7,8] The potentiation was found at 0.01 mmol per liter methyl xanthine, a concentration that blocks adenosine receptors but is lower than that required to inhibit phosphodiesterase.

Less experimental work has been done to find compounds that enhance odors. Aside from administration of steroids, the only practical approach thus far has been to add flavors to food for persons with hyposmia.[1] That is, carrot flavor is added to carrots, egg flavor to eggs and bean flavor to beans. These flavors are available through commercial flavor companies.

In conclusion, threshold measurements and identification tests are sufficient for diagnosing global chemosensory losses in a physician's office. Diagnosis and treatment of more subtle deficits, however, will ultimately require both a better understanding of the chemical senses and more sophisticated testing procedures.

SUSAN S. SCHIFFMAN, PhD
*Professor of Medical Psychology*
*Department of Psychiatry*
*Duke Medical Center*
*Durham, North Carolina*

**REFERENCES**

1. Schiffman SS: Taste and smell in disease. N Engl J Med 1983; 308:1275-1279, 1337-1343

2. Henkin RI: Olfaction in human disease, *In* English GM (Ed): Looseleaf Series of Otolaryngology. New York, Harper & Row, 1982, pp 1-39

3. Schiffman SS, Lindley MG, Clark TB, et al: Molecular mechanism of sweet taste: Relationship of hydrogen bonding to taste sensitivity for both young and elderly. Neurobiol Aging 1981; 2:173-185

4. Sklar PB, Anholt RRH, Snyder SH: The odorant-sensitive adenylate cyclase of olfactory receptor cells: Differential stimulation by distinct classes of odorants. J Biol Chem 1986; 261:15538-15543

5. Huque T, Bruch RC: Odorant- and guanine nucleotide-stimulated phosphoinositide turnover in olfactory cilia. Biochem Biophys Res Commun 1986; 137:36-42

6. Schiffman SS, Lockhead E, Maes FW: Amiloride reduces the taste intensity of $Na^+$ and $Li^+$ salts and sweeteners. Proc Natl Acad Sci USA 1983; 80:6136-6140

7. Schiffman SS, Gill JM, Diaz C: Methyl xanthines enhance taste: Evidence for modulation of taste by adenosine receptor. Pharmacol Biochem Behav 1985; 22:195-203

8. Schiffman SS, Diaz C, Beeker TG: Caffeine intensifies taste of certain sweeteners: Role of adenosine receptor. Pharmacol Biochem Behav 1986; 24:429-432

9. Kawamura Y, Kare MR (Eds): Umami: A Basic Taste. New York, Marcel Dekker, 1987

10. Schiffman SS, Simon SA, Gill JM, et al: Bretylium tosylate enhances salt taste. Physiol Behav 1986; 36:1129-1137

11. Bacaner M: Prophylaxis and therapy of ventricular fibrillation: Bretylium reviewed and licocaine refuted. Int J Cardiol 1983; 4:133-152

12. Ilani A, Lichtstein D, Bacaner MB: Bretylium opens mucosal amiloride-sensitive sodium channels. Biochim Biophys Acta 1982; 693:503-506

13. Ilani A, Yachin S, Lichtstein D: Comparison between bretylium and diphenylhydantoin interaction with mucosal sodium-channels. Biochim Biophys Acta 1984; 777:323-330

## Clinical Evaluation of Anemia

THE INTRODUCTION of electronic counting of blood cells into the routine clinical laboratory has been the greatest single advance in the routine laboratory evaluation of anemias since the introduction of the polychrome stains. The report of the modern complete blood count (CBC) contains a dazzling array of numbers derived from the analysis of a drop or two of blood. Many hematologists would agree that the probable cause of most anemias is indicated by the CBC, sometimes supplemented by the reticulocyte count. A few hematologists, spiritual denizens of an earlier time, look at the stained smears, but their number (the hematologists, that is, not the smears) is diminishing. A doctrine promulgated in Boston states that the examination of blood smears may safely be left to technologists, freeing hematologists for more profitable, if not more pleasurable, pursuits.[1] This sharing of the diagnostic prowess between technologist and physician has had a long tradition; it should be clearly understood, however, that the hematologist or physician must be well acquainted with the skills and experience of technologists to whom so much is entrusted. It will not do for administrators to budget for housekeeping aids to replace physicians in examining blood smears.

Elsewhere in this issue of the journal, Ralph Wallerstein, Jr, MD, has written a lucid exposition of the modern laboratory evaluation of anemia. It seems probable that the heresy about the peripheral smear has adherents in San Francisco because Dr Wallerstein appears to rank examination of the stained smear below the CBC and reticulocyte count.

Although electronic counting yields an accurate enumeration of red blood cells and hemoglobin is directly and rather precisely measured, most physicians continue to speak of the hematocrit, a test that would rapidly join the icteric index were it not kept alive, and indeed nurtured, by physicians trained in ages past. Ask a medical student, or for that matter a medical resident, about a patient's red blood cell count and you are likely to see a look of utter disbelief, as though you had asked for Osler's home telephone number.

Red blood cells were probably first counted in 1852, when values of about 5 million per $\mu$l were obtained by Nierodt. Subsequently, inaccuracies in routine counting caused the red blood cell count to fall into disrepute, and it was replaced by the hematocrit in the evaluation of anemia. Electronic blood counting, however, with accurate red blood cell counts has been available in hospital laboratories for more than two decades, yet the red blood cell count is still largely ignored by many physicians.

Ironically, the more highly regarded mean corpuscular hemoglobin and mean corpuscular volume are dependent on the red blood cell count. One might speculate that had the red blood cell count never been done in clinical laboratories until electronic counting became available, it would have been accepted by clinicians with enthusiasm. Many years will apparently be required for the count to live down its shady past. Yet, a 25-year-old Laotian man with a hemoglobin of 12 grams per dl and 6.5 million per $\mu$l red blood cells probably needs only a hemoglobin analysis to complete the workup of his microcytic anemia.

The common diagnostic problem in the analysis of modestly microcytic anemias is the association with chronic disease; Dr Wallerstein has addressed this problem in helpful detail. To his list of causes of microcytic anemia, one might add pyropoikilocytosis, an admittedly rare disorder, but one in which the diagnosis may be overlooked for many years.

In the analysis of macrocytic anemias, most physicians do not have access to the deoxyuridine suppression test, and its usefulness in a clinical laboratory remains to be evaluated. The measurement of gastric hydrochloric acid receives little mention now, although it can be valuable in evaluating megaloblastic anemia, particularly with pentagastrin stimulation. The absence of hydrochloric acid in gastric contents does not provide a definitive test in the elderly, but its presence rules out pernicious anemia (with the implication of lifelong monthly injections of vitamin $B_{12}$).

The Schilling test may be the gold standard in the diagnosis of pernicious anemia, but its accuracy is uncertain in many laboratories. Some laboratories have not been able to substitute counting of plasma for urine unless the isotope dosage was increased, and incomplete urine collections are regularly blamed for any problems that are encountered.

Many drugs used in the treatment of malignant disorders cause megaloblastic anemias, some by directly interfering with DNA synthesis, while others are folic acid antagonists, usually inhibiting dihydrofolate reductase. Other drugs, particularly anticonvulsants, occasionally lead to megaloblastosis by poorly understood interference with mechanisms of gastrointestinal absorption. Oral contraceptives have been rarely associated with folic acid deficiency. In view of the numerical decline in options for contraception, the risk of folic acid deficiency in association with oral contraceptives ought to be more clearly delineated.

In the analysis of hemolytic anemias, Dr Wallerstein recommends looking for hemoglobinuria; the examination of stool specimens for blood might be recommended as an equally immediate test in evaluating microcytic anemias. It is also not clear that sickle cell anemia "is obvious from the smear" to everyone. Sickle cell preparations or solubility tests are far better.

This review appears shortly after publication of an article in another journal indicating that the evaluation of anemia was not very competent in a significant proportion of medical inpatients in a university hospital.[2] Dr Wallerstein's article obviously deserves a wide readership.

Another (also recent) article emphasizes the lack of efficacy of CBCs in detecting disease of healthy people.[3] Any elderly university hematologist who taught presumably healthy medical students to do CBCs (on themselves) would certainly agree. It is also not clear, however, that consultation with physicians is a cost-effective method of disease detection in a healthy population. Perhaps the role of physicians should not be the enthusiastic search for disease in asymptomatic

healthy people for whom preventive medicine seems more appropriate. Smoking cessation clinics may be a lot more useful than serial blood counts of the healthy population.

Dr Wallerstein provides a useful review of the laboratory approach to anemia that has already been detected. The *clinical* evaluation will often shorten the laboratory evaluation a great deal: evaluation of the anemia of an alcoholic patient, or of a patient with bacterial endocarditis, may often be deferred because the anemia will disappear when the underlying illness is cured. The ready availability of laboratory tests makes possible sophisticated evaluations that may be unnecessary. The array of tests in a clinical laboratory is one of the achievements of modern clinical science. The critical and discriminating use of those tests should be another achievement: in most cases of anemia, the clinical evaluation begun with the history and physical examination followed by the modern CBC may require only a few additional laboratory tests.

HELEN M. RANNEY, MD
*Professor of Medicine*
*Department of Medicine*
*University of California, San Diego, School of Medicine*
*La Jolla*

REFERENCES

1. Jen P, Woo B, Rosenthal PE, et al: The value of the peripheral blood smear in anemia inpatients. Ann Intern Med 1983; 143:1120-1125

2. Self KG, Conrady MM, Eichner ER: Failure to diagnose anemia in medical inpatients. Am J Med 1986; 81:786-790

3. Shapiro MF, Greenfield S: The complete blood count and leukocyte differential count. Ann Intern Med 1987; 106:65-74

## Transient Ischemic Attacks

IN THIS ISSUE of the journal, Rothrock reminds us that transient ischemic attack (TIA) is an important risk factor for stroke. He also emphasizes that TIA is as important a warning of future myocardial infarction as of stroke, and that most persons who experience such an event do not suffer a subsequent stroke. Additionally, there is no ideal medical treatment for all TIAs, and surgical treatment is risky business. He argues that for these reasons, the often recommended aggressive approach to the evaluation and treatment of TIA should be restrained. Finally, Rothrock argues that TIA is a family of pathophysiologic disorders, each with its own natural history. Some TIAs are relatively benign while some warn of impending disaster. It follows that the aggressive use of high-risk therapy for benign TIA in an elderly patient with severe coronary artery disease is unwarranted. Alternatively, a nihilistic approach to a younger patient with a malignant TIA seems equally unwarranted. I agree generally with all of these assertions. I am less optimistic that we can determine the specific cause of most TIAs, and I am more optimistic about treatment.

Rothrock believes that much of our failure to demonstrate real benefit from various treatments for TIA and stroke has resulted from the tendency to lump together the diverse causes. There are indeed many causes of TIA and ischemic stroke, and I am a strong advocate for being clear in one's thinking and stringent in one's evaluation of patients in this regard. Nevertheless, the vast majority of TIAs occurring in elderly persons in western countries are caused by obstruction of large arteries by atherosclerosis and associated thrombi, obstruction of small arteries by lipohyalinosis and associated thrombi and embolic arterial obstruction arising from atherosclerotic debris from arteries in the chest or neck, or from thrombi in the heart. Rothrock believes we can tell one type from the other. I am less certain. The approach he outlines to making these distinctions is valid but it often falls far short. Once a fixed deficit appears—that is, an ischemic stroke occurs—it is more often possible to be certain, but even at autopsy one often cannot be certain of the pathophysiology. Nevertheless, it seems likely that the best treatments for the various causes of TIA will be different and that we must make as specific a diagnosis as possible when confronted with the "TIA syndrome" if we are to initiate appropriate specific treatment.

Again, Rothrock expresses concern that "much of our failure to show real benefit from various treatments for TIA and stroke has resulted from the tendency to 'lump together,' to regard TIA and stroke as diagnoses per se and not as syndromes with diverse causes." This may be true. It has been a major criticism of the extracranial-intracranial bypass study.[1] It seemed a few years ago (and still does!) to make excellent sense to take patients with cerebral ischemic symptoms and an inoperable obstruction in the carotid arterial system, and bypass the obstruction. Consequently, a large, multicenter study was carried out to determine if the operation is effective in preventing strokes in patients with recent hemispheric or retinal TIA or infarction who had atherosclerotic narrowing or occlusion of the ipsilateral internal carotid or middle cerebral artery. The study involved 1,377 patients randomly selected to "best medical care" (which included one aspirin given four times a day) versus "the same regimen plus bypass surgery joining the superficial temporal artery to the middle cerebral artery" and followed for an average of 56 months. The study methods were impeccable and the results were definitive. The operation failed to reduce the risk of ischemic stroke. Subsequently, it has been emphasized[2] that positron emission tomography has the ability to separate patients with symptomatic cerebral ischemia into three pathophysiologic states: those with (1) normal cerebrovascular physiology, (2) exhausted hemodynamic reserve and (3) impaired oxygen carriage reserve. Some hopeful investigators believe that revascularization applied to those patients with demonstrated hemodynamic impairment, rather than those selected on the less discriminatory clinical grounds that were used in the extracranial-intracranial bypass study, will prove to be beneficial. I doubt they are correct—but for several million dollars we could find out! It is true that several kinds of patients were lumped together in this study and randomization by the positron emission tomography strata noted above may have yielded different results—although analysis for a large number of theoretically important variables failed to show any group of patients who benefited from the surgical procedure. I am not criticizing the importance of randomly selecting patients by accurate and specific diagnoses, but many preconceived ideas are often incorporated in the "correct diagnosis."

I am less pessimistic that "aggressive treatment of a patient with [TIA] has little effect on reducing stroke incidence." I believe the weight of evidence favors the view that aspirin works! The question is how well, in whom and in what dose. Aggregate data[3] indicate that 1,300 mg given daily reduces the incidence of stroke by about 25% in men with TIA of recent onset or small stroke, and we will likely learn soon that 325 mg is equally as effective.[4] It appears to benefit women less, if at all. Sulfinpyrazone (Anturane) and dipyridamole have not proved effective in preventing atherothrombotic stroke.[4] Ticlopidine hydrochloride is a new plate-

let-antiaggregation agent that is currently being tested against aspirin for this indication in a large, multicenter, randomized and double-blind trial that will be completed in early 1988.[5] Perhaps its use will be beneficial, even in women.

Rothrock has reviewed the status of anticoagulation. A major focus in this regard in recent years has been on the rising risk of atrial fibrillation.[6] The incidence of this condition not due to rheumatic heart disease increases with increasing age and, by age 80 years, about 15% of Americans will be in atrial fibrillation.[7] The risk of stroke in these persons is the same as that for those with new-onset atherothrombotic TIA, about 6% per year—greater in the first year after onset for both atrial fibrillation and transient ischemic attack.[6] Although we can identify the population with atrial fibrillation at high risk for stroke, we do not know what treatment to recommend. Extrapolating from meager data regarding anticoagulation in patients with rheumatic atrial fibrillation, we believe anticoagulation may be effective. On the other hand, long-term anticoagulation of elderly patients, many of whom are hypertensive, is known to be hazardous. Thus we need to know if the benefits would outweigh the risks, even if anticoagulation were proved effective. Two multicenter studies in progress in the United States are investigating this issue. One is testing low-dose warfarin sodium administration against placebo and the other is testing giving low-dose warfarin versus low-dose aspirin versus placebo in a three-armed trial. It will be a few years before the results are available to guide us.

The role for carotid endarterectomy in preventing stroke is indeed unclear, yet the operation will be done approximately 180,000 times in the United States this year, half for asymptomatic carotid disease, at a cost of more than $1 billion. While the single randomized study of this procedure is interpreted by some writers to have suggested a benefit from the operation,[8] I and others[9] believe it showed no benefit. The results were not powerful, though. The number of patients studied was small and the trial method at the time was less stringent than we now demand. A lower operative morbidity and mortality are said to be achievable in recent years, but risk-factor management and antithrombotic therapy have also improved. For all of these reasons, the time is ripe for a proper evaluation of carotid endarterectomy in stroke prevention. Two prospective, multicenter studies of this procedure for asymptomatic stenosis are in progress. A similar study of carotid endarterectomy for preventing stroke in patients with TIA and minor stroke is being mounted. This study will stratify patients according to the type of arterial lesion they have on the grounds that different types of lesions may respond differently. It is hoped the results of these very important studies will define the role of carotid endarterectomy in stroke prevention.

Rothrock's review is a fair and balanced one. It reminds us that cerebral transient ischemic attacks are but one manifestation of generalized atherosclerosis that is usually present in a symptomatic patient. Consequently, major efforts should be directed toward modifying atherosclerosis risk factors, and restraint is warranted when considering how vigorous to be in the evaluation and management of TIA. A number of important old questions in TIA therapy are finally being addressed directly in major clinical studies, and definitive answers are imminent. Several new treatments are also on the horizon.

J. DONALD EASTON, MD
*Professor and Chair*
*Program in Neurology*
*Department of Neurology*
*Rhode Island Hospital-Brown University*
*Providence, RI*

**REFERENCES**

1. EC-IC Bypass Study Group: Failure of extracranial-intracranial arterial bypass to reduce the risk of ischemic stroke: Results of an international randomized trial. N Engl J Med 1985; 313:1191-1200

2. Frackowiak RSJ: PET scanning: Can it help resolve management issues in cerebral ischemic disease? Stroke 1986; 17:803-807

3. Easton JD, Hart RG, Sherman DG, et al: Diagnosis and management of ischemic stroke—Part I: Threatened stroke and its management. Curr Probl Cardiol 1983 Aug; 8:1-76

4. Peto R, Warlow CP: Aspirin and transient ischemic attacks. Br Med J 1979; 2:1291-1292

5. Hass WK, Bruno JJ, Molony BA, et al: Ticlopidine hydrochloride: A new approach to stroke prevention after TIA. *In* Meyer JS, Lechner H, Reivich M, et al (Eds): Cerebral Vascular Disease 4, 11th International Salzburg Conference. Amsterdam, Excerpta Medica, 1983, pp 134-137

6. Hart RG, Sherman DG, Miller VT, et al: Diagnosis and management of ischemic stroke—Part II: Selected controversies. Curr Probl Cardiol 1983 Oct; 8:1-77

7. Wolf PA, Kannel WB, Abbott RD: Atrial fibrillation and stroke in the elderly, the Framingham Study (Abstr). Stroke 1985; 16:138

8. Fields WS, Maslenikov V, Meyer JS, et al: Joint study of extracranial arterial occlusion—V. Progress report of prognosis following surgery or nonsurgical treatment for transient cerebral ischemic attacks and cervical carotid artery lesions. JAMA 1970; 211:1993-2003

9. Hass WK, Jonas S: Caution falling rock zone: An analysis of the medical and surgical management of threatened stroke. Proc Inst Med Chi 1980; 33:80-84

## It Can Be a Lethal Instrument

ELSEWHERE in this issue Sewell and colleagues report on "Injuries and Fatalities Associated With Off-Road Three Wheeled All-Terrain Vehicles." These vehicles look like oversized tricycles but they are motorized vehicles, and they are not toys. They are fast, powerful, unstable and may be difficult to control. Their use has led to an alarming number of injuries and fatalities and this number is increasing. More than a third of the injuries and almost half the deaths are reported to have occurred in children under 12 years of age.

Accidents with these vehicles result from a number of causes. Climbing a hill, rounding a corner, swerving to miss an obstacle or hitting a bump, ditch or obstruction, can cause the vehicle to overturn forward, backward or sideways, with the rider thrown from the seat or pinned beneath the vehicle. These are not machines that are safe, for young people especially. Their operation requires careful training and quick decisions involving steering, shifts of weight and adjustments of hand and foot controls. This is certainly not child's play!

Ought not there to be a law?

MSMW

# Case Reports

## Myasthenia Gravis and Hyperthyrotropinemia in a Child

SUSAN M. SCOTT, MD
*Albuquerque*

ALAN H. KLEIN, MD
JO ANNE BRASEL, MD
*Torrance, California*

THE SYNDROME of inappropriate secretion of thyrotropin, defined by elevated thyroid-stimulating hormone (TSH) levels with clinical hyperthyroidism, was first described in 1972.[1] Since then fewer than 40 patients have been found to have this syndrome,[2-6] and most childhood cases have been recognized because of an affected proband adult. Early reports were primarily of patients with elevated TSH levels and pituitary tumors.[7-10] With increasing recognition of this syndrome as a cause of hyperthyroidism, more idiopathic cases have been reported. We now describe the case of a 5-year-old boy with ocular myasthenia gravis and hyperthyroidism who had elevated TSH levels with clinical hyperthyroidism.

### Report of a Case

The patient presented at 5 years of age with bilateral ptosis and hyperactive behavior. His mother said these symptoms began a week before presentation. A diagnosis of myasthenia gravis was based on high titers to anti-acetylcholine receptor antibody and a positive response to the administration of edrophonium chloride (Tensilon). Physical signs of hyperthyroidism were tachycardia, a wide pulse pressure and hyperactive behavior. In addition, his thyroid gland was enlarged, measuring 7 by 5 cm across the length of each lobe and 2.5 cm across the width of the isthmus. These measurements are two to three times the linear measurements expected. There were no eye signs suggestive of the autoimmune eye disease found in Graves' disease nor evidence of the increased sympathetic tone of hyperthyroidism—that is, the extraocular muscles were normal in movement and mass, the eyeball was in normal position and there was no stare. Laboratory tests showed elevated serum thyroxine ($T_4$) and triiodothyronine ($T_3$) levels, increased radioiodine uptake (RIU), a positive perchlorate discharge test and low titers of antithyroid antibodies. With a diagnosis of probable combined hyperthyroidism and Hashimoto's thyroiditis, a regimen of methimazole was started (Table 1). Over the next two years of antithyroid therapy, elevated serum TSH concentrations were noted with clinical hyperthyroidism (increased pulse pressure, hyperactive behavior and poor weight gain). Signs of systemic myasthenia gravis failed to develop, but the ocular myasthenia continued to respond poorly to large doses of pyridostigmine bromide (Mestinon) while he had hyperthyroidism. Several measurements of antithyroid antibodies and of thyroid-stimulating immunoglobulins (TSI) were made, which were all negative.

Twenty months after treatment began, we initiated studies of his pituitary-thyroid axis. Skull films and a computed tomographic (CT) scan were done and all thyroid-related drug therapy was discontinued for three weeks. He was then placed on a regimen of triiodothyronine (liothyronine

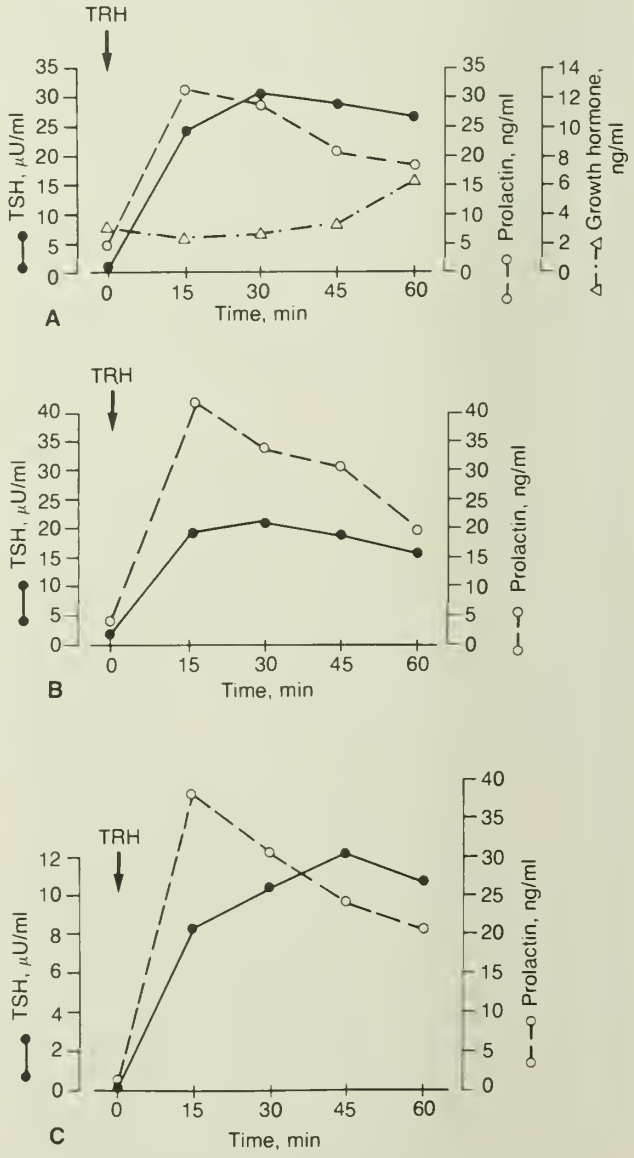



**Figure 1.—A,** Response of thyroid-stimulating hormone (TSH) (●—●), prolactin (○ - - ○) and growth hormone (△ - · - △) to thyrotropin-releasing hormone (TRH) when the patient's thyroxine ($T_4$) level was 23.0 μg per dl, triiodothyronine level 320 ng per dl and TSH concentration < 2 μU per ml and he was off all thyroid-related drug therapy. **B,** Response of TSH (●—●) and prolactin (○ - - ○) to TRH when the patient's $T_4$ level was 10.0 μg per dl and TSH concentration < 1.0 μU per ml and he had received liothyronine sodium (Cytomel), 20 μg 3 times a day for 10 days. **C,** Response of TSH (●—●) and prolactin (○ - - ○) to TRH when the patient's $T_4$ level was 10.0 μg per dl, $T_3$ was 330 ng per dl and TSH concentration 4.0 μU per ml and he had been receiving liothyronine for 5 months. The TSH scale is changed from that in **A** and **B.**

(Scott SM, Klein AH, Brasel JA: Myasthenia gravis and hyperthyrotropinemia in a child. West J Med 1987 Apr; 146:476-479)

From the Department of Pediatrics, University of New Mexico School of Medicine, Albuquerque (Dr Scott); the Department of Pediatrics, Cedars-Sinai Medical Center, Los Angeles (Dr Klein), and the Department of Pediatrics, Harbor-UCLA Medical Center, Torrance, California (Dr Brasel).

This information was presented in the form of a poster at the Midwest Society of Pediatric Research Meeting, Chicago, November, 1983.

Reprint requests to Susan M. Scott, MD, Department of Pediatrics, University of New Mexico School of Medicine, Albuquerque, NM 87131.

ABBREVIATIONS USED IN TEXT

CT = computed tomography
RIU = radioiodine uptake
RIA = radioimmunoassay
$T_3$ = triiodothyronine
$T_4$ = thyroxine
TRH = thyrotropin-releasing hormone
TSH = thyroid-stimulating hormone
TSI = thyroid-stimulating immunoglobulin

sodium [Cytomel]), 20 mg three times a day for ten days. After each manipulation of his thyroid state, an RIU test and a thyrotropin-releasing hormone (TRH) test were done (Figure 1-A and -B). Growth hormone and prolactin responses to TRH were also measured. At the completion of the testing, the patient was placed on long-term triiodothyronine therapy (20 mg three times a day). He began to gain weight more appropriately, his pulse pressure decreased and his behavior improved. Also, his ptosis resolved on the same dose of pyridostigmine. Attempts to discontinue the pyridostigmine therapy while the patient was euthyroid led to aggravation of his symptoms. After five months of therapy, a TRH test was repeated (Figure 1-C).

## Laboratory Methods

Serum total $T_4$ and $T_3$ concentrations were measured by radioimmunoassay (RIA). The normal range of values for $T_4$ is 5.0 to 13.0 $\mu$g per dl and for $T_3$ is 80 to 230 ng per dl. The serum TSH level was measured by radioimmunoassay with a sensitivity of 0.2 $\mu$U per ml. The normal range for human TSH levels with this method is less than 5 $\mu$U per ml. The TSI measurement was done in the laboratory of Basil Rapoport, MD (University of California, San Francisco), according to the method described by Hinds and co-workers.[11] Antimicrosomal and antithyroglobulin antithyroid antibodies were measured by the method of Riott and Doniach.[12] The TRH test was done in the fasting state; TRH (500 $\mu$g) was given intravenously slowly over five minutes and blood specimens collected at base line and 30, 45 and 60 minutes for TSH, growth hormone and prolactin measurements. Prolactin and growth hormone levels were also measured by RIA; the normal ranges are 0 to 25 ng per ml and 0 to 5 ng per ml, respectively. The normal response to TRH is a change in serum TSH concentration from a base line of 2 to 25 $\mu$U per ml at 30 minutes. The perchlorate discharge test was done by giving 120 mg per kg potassium perchlorate two hours after a dose of sodium iodide I 123. A normal $^{123}I$ discharge from the thyroid gland at two hours is less than 10%.

## Results and Discussion

At the time of diagnosis (Table 1), the patient had clinical hyperthyroidism. Further, the thyroid gland was firm and

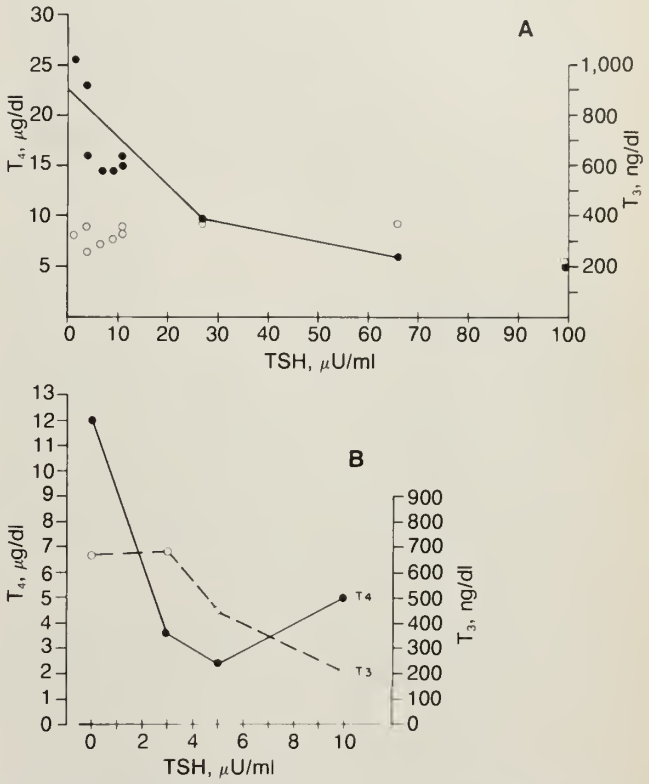



**Figure 2.—A,** Relationship between thyroxine ($T_4$) and thyroid-stimulating hormone (TSH) levels (●—●) and ($T_3$) and TSH levels (○ - - ○) before liothyronine sodium (Cytomel) therapy is started. **B,** Relationship between $T_4$ (●—●) and $T_3$ (○ - - ○) levels with TSH while patient is on liothyronine therapy.

TABLE 1.—*Data Sheet of Patient's Therapy During First 20 Months After Diagnosis*

| *Time, mo* | *Thyroid Test Values* $T_4$, µg/dl | $T_3$, ng/dl | TSH, µU/ml | *Others* |
|---|---|---|---|---|
| Dx .... | 24.6 | 320 | 1.5 | Anti-acetylcholine receptor Ab 0.6; microsomal Ab 1:100; thyroglobulin Ab 1:10; TSI* θ; CT scan normal; ANA θ; RIU: 2 h 20%, 4 h 30%, 6 h 37%, 24 h 50%; perchlorate discharge 28% |
| ↓ | Antithyroid medications, methimazole, 5 mg BID | | | |
| 3 .... | 15.0 | 390 | 11.7 | |
| 4 .... | 7.9 | 297 | >40 | |
| 6 .... | 8.1 | 310 | >40 | |
| 8 .... | 7.0 | 365 | 66 | |
| 9 .... | 14.0 | 281 | 7.3 | Microsomal Ab θ, thyroglobulin Ab θ |
| 10 .... | 17.2 | 324 | 11.6 | |
| 13 .... | 17.0 | 255 | 4.6 | |
| ↓ | Methimazole, 5 mg TID | | | |
| 14 .... | 14.0 | 305 | 9.7 | |
| 16 .... | 9.8 | 364 | 27.3 | Anti-TSH Ab θ, TSI* θ, microsomal Ab θ, thyroglobulin Ab θ |
| ↓ | Methimazole, 15 mg TID | | | |
| 20 .... | 0.4 | 132 | >50 | |

Ab=antibody, ANA=antinuclear antibody, BID=twice a day, CT=computed tomography, RIU=radioiodine uptake, $T_3$=triiodothyronine, $T_4$=thyroxine, TID=3 times a day, TSH=thyroid-stimulating hormone, TSI=thyroid-stimulating immunoglobulin, θ=negative

*The TSI was done at the laboratory of Basil Rapoport, MD, at University of California, San Francisco.

bosselated, and there was a positive perchlorate discharge test. These observations, plus the low thyroid antibody titers, are compatible with a diagnosis of combined hyperthyroidism and Hashimoto's thyroiditis in childhood.[13] The associated high titer for anti-acethylcholine receptor antibody suggested autoimmune disease as the patient's underlying problem, although subsequent antithyroid antibody titers and TSI levels were negative. No TSH antibody was detected as the serum TSH diluted in parallel with human TSH reference material in a homologous RIA. Inappropriately elevated levels of the $\alpha$-subunit are not suggested as this RIA generated against the intact $\alpha, \beta$ TSH molecule had insignificant cross-reaction with intact follicle-stimulating and luteinizing hormones whose subunits are also available for reaction. Thus, it is unclear if autoimmune thyroiditis was present at diagnosis, but there was no convincing evidence that it was present at the time of the studies of his pituitary-thyroid axis.

Our studies were prompted by a measurable and frequently elevated TSH level with elevated $T_4$ and $T_3$ levels and clinical hyperthyroidism. We chose to study the TSH response to TRH because the pattern of pituitary secretion of TSH in response to TRH is well described in patients with perturbations in their thyroid state. Thus, with our patient off all medication therapy and clinically hyperthyroid, his pituitary responded as though it were in a euthyroid environment and secreted TSH in a normal pattern. This result might have been predicted from the observation that suppression of his TSH was associated with serum $T_4$ concentrations above 15 $\mu$g per dl (Figure 2-A). Thus, his pituitary sensed a serum $T_4$ level greater than 15 $\mu$g per dl as normal.

Figure 1-B shows the pituitary response to TRH after the patient was placed on a regimen of liothyronine. Using the same dose of TRH, the peak TSH response was decreased, implying some suppression of TSH secretion by the exogenous triiodothyronine therapy. At the same time that the TSH response to TRH was decreased, the serum TSH concentration was suppressed, and the $T_4$ level had fallen from 23 to 10 $\mu$g per dl. Immunoglobulin-dependent hyperthyroidism would not have been suppressed by exogenous $T_3$, suggesting a mechanism for the hyperthyroidism that was responsive to thyroid hormones but at elevated concentrations.

The continued elevation of TSH concentrations with normal to elevated serum thyroid hormone levels indicates a decreased pituitary sensitivity to thyroid hormones. This pituitary insensitivity may also include the lactotropes. The prolactin response to TRH is ordinarily affected by thyroid hormone concentrations in a parallel fashion to the TSH response.[14] Therefore, a blunted prolactin response would be expected in the presence of a serum $T_4$ level of 23.0 $\mu$g per dl, rather than the normal response seen (Figure 1-A). The prolactin response, however, did not change as the TSH response did with liothyronine therapy. In patients with pituitary tumors secreting TSH, a release of growth hormone by TRH stimulation has occasionally been documented, implying the involvement of the somatotropes in the tumors.[8] Our patient did not have release of growth hormone with TRH stimulation (Figure 1-A). Also, no abnormality of the sella turcica was observed by x-ray examination or CT scan. These observations, combined with the suppressibility of TSH by exogenous triiodothyronine (Figure 1-B and 1-C), suggests pituitary insensitivity as the cause of this patient's hyperthyroidism, rather than a TSH-secreting tumor.

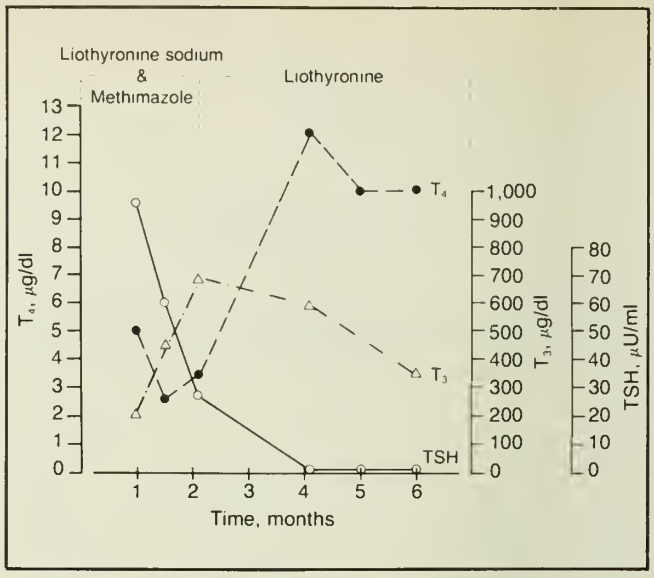



**Figure 3.**—Relationship between thyroxine ($T_4$) (●--●), thyroid-stimulating hormone (TSH) (○—○) and triiodothyronine ($T_3$) (△-·-△) levels with time while the patient was on liothyronine sodium and methimazole therapy followed by a regimen of liothyronine alone. The normal reference ranges for $T_4$, TSH and $T_3$ are given in the text.

Hormone treatment of TSH-dependent, nontumor hyperthyroidism was reported by Rosler and associates,[15] suggesting that a single daily dose of exogenous triiodothyronine may reestablish normal thyroid function. In the present case, after long-term liothyronine treatment, serum $T_4$ and $T_3$ levels returned to normal, as did the relationship of the $T_4$ level to TSH concentrations (Figure 2-B). Figure 3 shows the course of serum $T_4$, $T_3$ and TSH levels over six months of treatment with liothyronine. When the liothyronine dose was briefly decreased, his TSH and $T_4$ levels increased promptly; there was a more delayed increase in the serum $T_3$ level (data not shown).

## Summary and Conclusions

This case shows a fascinating and puzzling clinical condition. The patient presented with clinical and biochemical features suggesting autoimmune thyroid and neuromuscular junction disease. His hyperthyroidism was difficult to control on the usual dose of methimazole, but large doses did decrease the serum $T_4$ level into the normal range. This led to an increase in serum TSH concentrations, an increase in the size of his gland and finally to an increase in his serum $T_4$ level with a worsening of his clinical course. When his $T_4$ and $T_3$ levels were allowed to rise to suppress his TSH, he became clinically hyperthyroid. These observations, together with a normal TSH response to TRH in the presence of clinical hyperthyroidism, indicate that the pituitary set point for TSH secretion is abnormal in this 5-year-old boy. The patient's thyroid disorder is certainly distinct from classical Graves' disease because he appears to have pituitary thyrotrope resistance to thyroid hormones. We suggest that in patients where the response to antithyroid medication is unusual and serum TSH levels are noted to be inappropriately elevated, the appropriate therapy for the hyperthyroidism may, in fact, be triiodothyronine.

### REFERENCES

1. Emerson CH, Utiger RD: Hyperthyroidism and excessive thyrotropin secretion. N Engl J Med 1972; 287:328-333

2. Gharib M, Carpenter PC, Scheithauer BW, et al: The spectrum of inappro-

priate pituitary thyrotropin secretion associated with hyperthyroidism. Mayo Clin Proc 1982; 57:556-563

3. Gershengorn MC, Weintraub BD: Thyrotropin-induced hyperthyroidism caused by selective pituitary resistance to thyroid hormone—A new syndrome of 'inappropriate secretion of TSH.' J Clin Invest 1975; 56:633-642

4. Elewaut A, Mussche M, Vermeulen A: Familial partial target organ resistance to thyroid hormones. J Clin Endocrinol Metab 1976; 43:575-581

5. Smallridge RC, Wartofsky L, Dimond RC: Inappropriate secretion of thyrotropin: Discordance between the suppressive effects of corticosteroids and thyroid hormone. J Clin Endocrinol Metab 1979; 48:700-705

6. Kourides IA, Pekonen F, Weintraub BD: Absence of thyroid-binding immunoglobulins in patients with thyrotropin-mediated hyperthyroidism. J Clin Endocrinol Metab 1980; 51:272-274

7. Kourides IA, Ridgway EC, Weintraub BD, et al: Thyrotropin-induced hyperthyroidism: Use of alpha and beta subunit levels to identify patients with pituitary tumors. J Clin Endocrinol Metab 1977; 45:534-543

8. Lamberg BA, Pekonen F, Gordin A: TSH-induced hyperthyroidism and acromegaly due to pituitary tumour (Abstr). Ann Endocrinol 1978; 39:14A

9. Baylis PH: Case of hyperthyroidism due to a chromophobe adenoma. Clin Endocrinol (Oxf) 1976; 5:145-150

10. Faglia G, Ferrari C, Neri V, et al: High plasma thyrotropin levels in two patients with pituitary tumour. Acta Endocrinol (Copenh) 1972; 69:649-658

11. Hinds WE, Takai N, Rapoport B, et al: Thyroid-stimulating immunoglobulin bioassay using cultured human thyroid cells. J Clin Endocrinol Metab 1981; 52:1204-1210

12. Riott IM, Doniach D: World Health Organization Handbook of Immunological Techniques. Geneva, WHO, 1966, p 1

13. Rallison ML, Dobyns BM, Keating FR, et al: Occurrence and natural history of chronic lymphocytic thyroiditis in childhood. J Pediatr 1975; 86:675-682

14. Bowers CY, Friesen HG, Hwang P, et al: Prolactin and thyrotropin release in man by synthetic pyroglutamyl-histidyl-prolinamide. Biochem Biophys Res Commun 1971; 45:1033-1041

15. Rösler A, Litvin Y, Hage C, et al: Familial hyperthyroidism due to inappropriate thyrotropin secretion successfully treated with triiodothyronine. J Clin Endocrinol Metab 1982; 54:76-82

# *Streptococcus sanguis II* (Viridans) Prosthetic Valve Endocarditis With Myocardial, Splenic and Cerebral Abscesses

STEPHEN G. YOUNG, MD
*San Francisco*

THOMAS DAVEE, MD
JOSHUA FIERER, MD
MITCH K. MOREY, MD
*San Diego*

BACTERIAL ENDOCARDITIS of native and prosthetic heart valves is frequently caused by the viridans group of streptococci. Viridans streptococci are usually sensitive to penicillin, and they are rarely invasive and rarely cause destruction of extracardiac tissue. As a result of these characteristics, bacterial endocarditis caused by this group of bacteria is associated with less mortality and morbidity than endocarditis caused by other organisms.[1-3] *Streptococcus sanguis* is one of the most common species of viridans streptococci causing endocarditis.[4] We present here a fatal case of *S sanguis* prosthetic valve endocarditis that was associated with persistent fever, leukocytosis and myocardial, cerebral and splenic abscesses. This case shows that endocarditis due to *S sanguis* may be associated with an aggressive clinical course.

(Young SG, Davee T, Fierer J, et al: *Streptococcus sanguis II* [viridans] prosthetic valve endocarditis with myocardial, splenic and cerebral abscesses. West J Med 1987 Apr; 146:479-481)

From the Cardiology Division, Veterans Administration Medical Center, San Diego, and the Department of Medicine, University of California, San Diego, School of Medicine. Dr Young is now with the Gladstone Foundation Laboratory, San Francisco.

Reprint requests to Stephen G. Young, MD, Gladstone Foundation Laboratory, PO Box 40608, San Francisco, CA 94140.

## Report of a Case

The patient, a 64-year-old man, was admitted with a complaint of fatigue, fever and chills of five days' duration. Two years before admission, an Ionescu-Shiley aortic valve prosthesis was implanted because of calcific aortic stenosis and a dual-chamber pacemaker was implanted for perioperative heart block. On admission, the patient was oriented but lethargic, with a temperature of 36°C (96.8°F) and a respiratory rate of 25 per minute. There was one conjunctival hemorrhage, but no Roth spots were seen on funduscopic examination, and no cutaneous signs of endocarditis were observed on the hands or the feet. The jugular venous pressure was normal and on examination of the chest scattered rhonchi were heard. A systolic murmur consistent with the prosthetic aortic valve was noted, but there were no diastolic murmurs or gallops. There was no abdominal tenderness or hepatosplenomegaly.

A urinalysis showed microscopic hematuria. The hematocrit was 36% and leukocyte count was 16,300 per $\mu$l with 77% segmented forms, 7% band forms, 14% lymphocytes and 2% monocytes. The serum creatinine level was 4.0 mg per dl. The electrocardiogram showed a paced rhythm, and the chest x-ray film showed mild cardiomegaly without evidence of pulmonary venous congestion. An echocardiogram and Doppler study did not show any valvular vegetations or evidence of valvular regurgitation initially or later during the hospital course. Three of three blood cultures grew viridans streptococci, sensitive to penicillin (minimum bactericidal concentration $< 0.1$ $\mu$g per ml). On subsequent characterization with conventional media and API Rapid Strep (Analytab Products, Inc, Plainview, NY), it was identified as *S sanguis II*.

Antibiotic therapy with penicillin G (6 million units per day) and gentamicin sulfate was begun. Repeat blood cultures were consistently negative. Despite antibiotic therapy, the patient continued to have daily febrile episodes with temperatures of 38.8°C to 39.4°C (102°F to 103°F) throughout the hospital course. The leukocyte count remained between 15,000 and 30,000 per $\mu$l. On day 2, his mental status deteriorated to stupor, and on day 5 a right hemiparesis and seizures developed. A computed tomographic (CT) scan of the head revealed bilateral cerebral emboli. There were many petechiae on the feet and hands and new petechial lesions appeared throughout his hospital course. On day 13, biplanar ascending aortography showed a multiloculated perivalvular abscess extending below the prosthetic valve ring (Figure 1), but there was no aortic regurgitation. No left ventriculogram was done. A repeat CT scan of the head on the same day revealed multiple contrast-enhancing cerebral lesions, consistent with new embolic events, and a CT scan of the abdomen showed several large splenic abscesses.

To investigate the possibility that infection with another organism besides *S sanguis* accounted for the aggressive course of the illness, a percutaneous aspiration of one of the splenic abscesses was done. Serosanguineous material containing many polymorphonuclear leukocytes and Gram-positive cocci was obtained, but the culture of this material was sterile, even though penicillinase was added to the agar. Within three hours of the splenic aspiration, a fever to 39°C

(102°F) and hypotension developed and the patient had a pronounced reduction in the calculated systemic vascular resistance. There was no evidence of intraperitoneal bleeding. Respiratory and renal failure ensued, and the patient died on the 21st hospital day. Throughout the hospital course there was continued evidence of recurrent peripheral emboli. At no time during the hospital course did the patient have aortic regurgitation or congestive heart failure.

On postmortem examination there was a large myocardial abscess beneath the prosthetic aortic valve and a sinus tract extending from an abscess cavity in the interventricular septum to the pulmonary artery. Vegetations were noted on the prosthetic aortic valve cusps, the anterior leaflet of the mitral valve and the tricuspid leaflets. The spleen showed several large abscess cavities (Figure 2). The brain showed evidence of multiple thromboembolic lesions with microabscess cavities and masses of bacteria surrounding several arteries. Postmortem cultures of the heart valve and spleen did not yield *S sanguis*.

## Discussion

Viridans streptococci are a frequent cause of bacterial endocarditis, both on native valves and prosthetic heart valves, especially on prosthetic valves that have been in place for more than two months.[1-6] In general, patients with these infections respond well to antibiotic therapy and have an excellent prognosis.[1-3,5,6] The main reasons for this excellent prognosis are that viridans streptococci are usually sensitive to penicillin and they rarely invade tissue or form abscesses. Not surprisingly, the cure rate is somewhat lower if a prosthetic valve is infected,[5,6] but even in such cases it is rare for there to be suppurative extracardiac lesions.[3] What distinguished this case of viridans streptococcal endocarditis was the occurrence of multiple splenic abscesses and numerous microscopic brain abscesses. There was also an extensive myocardial abscess, but this complication is known to occur occasionally with prosthetic valve infections, even with relatively avirulent bacteria.[5,7]

It is generally believed that viridans streptococci cannot cause serious extracardiac infections because they are killed by normal host defenses. The relatively avascular heart valve and the fibrin-platelet nidus that precedes infection are areas of the body wherein an inflammatory infiltrate that allows bacteria to proliferate cannot form.[8,9] Despite the release of millions of bacteria from vegetations each day,[10,11] metastatic infection is rare with viridans streptococci and most of the extracardiac damage is due to either emboli or immune-complex vasculitis.[3,9] The only viridans streptococci that are exceptions to this rule are *Streptococcus pneumoniae*[12] and *Streptococcus milleri*.[13] Both of these organisms can be invasive and form abscesses, and endocarditis due to these organisms can be aggressive. *S pneumoniae* organisms are invasive in part because they are protected from phagocytosis by a polysaccharide capsule.[14] *S milleri* has been reported to produce parenchymal abscesses even in the absence of endocarditis.[13,15,16] Their virulence factors are still poorly understood. Although the taxonomic classification of viridans streptococci is still somewhat unsettled, the infecting organism in this case was a typical *S sanguis II* and not *S milleri*.

*S sanguis* has not been previously reported to have invasive characteristics. Hosea reported three cases of viridans endocarditis associated with abscesses and tissue invasion, but the species of the $\alpha$-hemolytic streptococci were not reported.[17] Arnett and Roberts[7] and Karchmer and co-workers[5] have reported the occurrence of valve ring abscesses or uncontrolled infection (or both) with viridans streptococci, but neither antibiotic sensitivity nor the exact species of the organisms was reported. The remarkable aspect of our case was that *S sanguis* infection was associated with both myocardial and peripheral abscess formation despite the fact that the organism was exquisitely sensitive to penicillin.

The most common indication for surgical intervention in endocarditis is congestive heart failure, usually a result of acute valvular regurgitation.[18-20] Infection of a prosthetic valve with a virulent or aggressive organism or an organism that is relatively resistant to antibiotics is an indication for surgical intervention.[1,5,6] Surgical intervention in this case was delayed because the patient had no valvular regurgitation or congestive heart failure and because we had identified the infecting organism as *S sanguis II* and knew that it was sensi-

**Figure 1.**—Right anterior oblique ascending aortogram. Injection of contrast material into the ascending aorta showed a normal ascending aorta **(Ao)** and no evidence of aortic valve regurgitation. A small multiloculated abscess cavity **(Ab)** could be seen beneath the prosthetic aortic valve. Further angiographic studies showed that the abscess did not involve the origin of the right coronary artery **(RCA)**.

**Figure 2.**—The photograph shows the spleen at necropsy. A large abscess cavity is seen in this section of the spleen. Other abscess cavities were seen in other sections of the spleen.

tive to penicillin. The persistent fever, however, suggested uncontrolled infection, even though all blood cultures after therapy were negative. Karchmer and colleagues found that fever lasting more than nine days after initiation of therapy was associated with a high incidence of myocardial abscess and a poor prognosis, as it was in this case.[5] Unfortunately, our patient sustained severe neurologic damage from multiple embolic events before surgical treatment could be undertaken. Had the cardiac abscess been identified earlier, a cardiac operation might have prevented the cerebral emboli.

This patient had numerous splenic abscesses on the computed tomographic scan of the abdomen. Johnson and coworkers have suggested that computed tomography is the best radiographic modality for detecting splenic abscesses.[21] Splenic abscesses occur occasionally in patients with infective endocarditis, but they are extremely rare with viridans streptococci.[22] In general, treatment of splenic abscesses associated with endocarditis requires splenectomy and antibiotic therapy; antibiotic therapy alone is not sufficient.[22] Whether our patient would have recovered from the splenic abscesses without an abdominal operation is uncertain. It is likely, however, that the abscesses in this patient would have been cured by antibiotic therapy alone because they were sterile when aspirated on day 13 of treatment and bacteria could not be cultured from the spleen at the postmortem examination.

## Conclusions

*S sanguis II*, a viridans streptococcus, may be associated with tissue invasion and abscess formation in a case of prosthetic valve endocarditis. Persistent fever and leukocytosis with multiple embolic events should prompt consideration of surgical intervention, even in the absence of positive blood cultures, valve dysfunction or congestive heart failure.

### REFERENCES


1. Garvey GJ, Neu HC: Infective endocarditis—An evolving disease. Medicine (Baltimore) 1978; 57:105-127

2. McNeill KM, Strong JE Jr, Lockwood WR: Bacterial endocarditis: An analysis of factors affecting long-term survival. Am Heart J 1978; 95:448-453

3. Weinstein L: Infective endocarditis, *In* E Braunwald (Ed): Heart Disease: A Textbook of Cardiovascular Medicine, 2nd Ed. Philadelphia, WB Saunders, 1984, pp 1136-1182

4. Roberts RB, Krieger AG, Schiller NL, et al: Viridans streptococcal endocarditis—The role of various species, including pyridoxal-dependent streptococci. Rev Infect Dis 1979; 1:955-965

5. Karchmer AW, Dismukes WE, Buckley MJ, et al: Late prosthetic valve endocarditis. Am J Med 1978; 64:199-206

6. Masur H, Johnson WD Jr: Prosthetic valve endocarditis. J Thorac Cardiovasc Surg 1980; 80:31-37

7. Arnett EN, Roberts WC: Valve ring abscess in active infective endocarditis. Circulation 1976; 54:140-145

8. Freedman LW: Infective Endocarditis and Other Intravascular Infections. New York, Plenum Medical Book, 1982, pp 9-55

9. Scheld MW: Pathogenesis and pathophysiology of infective endocarditis, *In* Sande MA, Kaye D, Root RK (Eds): Endocarditis. New York, Churchill Livingstone, 1984, pp 1-32

10. Werner AS, Cobbs CG, Kaye D, et al: Studies on the bacteremia of bacterial endocarditis. JAMA 1967; 202:199-203

11. Beeson PB, Brannon ES, Warren JV: Observations on the sites of removal of bacteria from the blood in patients with bacterial endocarditis. J Exp Med 1945; 1:9-23

12. Ruegsegger JM: Pneumococcal endocarditis. Am Heart J 1958; 56:867-877

13. Parker MT, Ball LC: Streptococci and aerococci associated with systemic infection in man. J Med Microbiol 1976; 9:275-301

14. McLeod CM, Krauss MR: Relation of virulence of pneumococcal strains for mice to the quantity of capsular polysaccharide formed in vitro. J Exp Med 1950; 92:1-9

15. Shlaes DM, Lerner PI, Wolinsky E, et al: Infections due to Lancefield group F and related streptococci (*S milleri, S anginosus*). Medicine (Baltimore) 1981; 60:197-207

16. Murray HW, Gross KC, Masur H, et al: Serious infections caused by *Streptococcus milleri*. Am J Med 1978; 64:759-764

17. Hosea SW: Virulent *Streptococcus viridans* bacterial endocarditis. Am Heart J 1981; 101:174-176

18. Dinubile MJ: Surgery in active endocarditis. Ann Intern Med 1982; 96:650-659

19. Dismukes WE: Management of infective endocarditis. Cardiovasc Clin 1981; 11:189-208

20. Richardson JV, Karp RB, Kirklin JW, et al: Treatment of infective endocarditis: A 10 year comparative analysis. Circulation 1978; 58:589-597

21. Johnson JD, Raff MJ, Drasin GF, et al: Radiology in the diagnosis of splenic abscess. Rev Infect Dis 1985; 7:10-20

22. Johnson JD, Raff MJ, Barnwell PA, et al: Splenic abscess complicating infectious endocarditis. Arch Intern Med 1983; 143:906-912


# Sarcoidosis Presenting as Chronic Thrombocytopenia


STEPHEN K. FIELD, MD, FRCP(C)
MAN-CHIU POON, MD
*Calgary, Alberta*


THROMBOCYTOPENIA is a rare complication of sarcoidosis. It may be immune in origin,[1] but increased platelet-associated immunoglobulin (Ig) G levels has been reported in only three previous cases.[2-4] We present a case of a patient with sarcoidosis and chronic thrombocytopenia with increased platelet-associated IgG levels.

## Report of a Case

The patient, a 23-year-old man, was admitted to hospital in August 1983 for investigation of thrombocytopenia. The patient first came to medical attention when a large thigh hematoma developed in 1977. His platelet count was $63 \times 10^9$ per liter at that time. The hemoglobin and leukocyte counts were normal. No other laboratory tests were done.

A knee operation in 1979 was uncomplicated, at which time his hemoglobin value and leukocyte count were normal. Platelets were not counted.

This admission was for drainage of a supraorbital hematoma. The patient said he did not have easy bruising or abnormal bleeding aside from these two episodes. He also said he did not have other health problems and was not taking medications. Apart from the hematoma, a physical examination showed no abnormalities.

The platelet count was $16 \times 10^9$ per liter. The hemoglobin level was 2.53 mmol per liter (16.3 grams per dl), the leukocyte count was $6.5 \times 10^9$ per liter with a normal differential, and giant platelets were noted on the blood smear. A bone marrow aspirate and a biopsy specimen showed megakaryocytic hyperplasia. The value of platelet-associated IgG, assayed by a radial immunodiffusion technique,[4] was 9.9 fg per platelet (normal $3.1 \pm 2.6$ fg per platelet; mean $\pm$ standard deviation). The prothrombin time and partial thromboplastin time were normal. A chest roentgenogram showed bilateral hilar adenopathy. Pulmonary function and serum angiotensin-converting enzyme and serum calcium levels were normal.

(Field SK, Poon MC: Sarcoidosis presenting as chronic thrombocytopenia. West J Med 1987 Apr; 146:481-482)


From the Pulmonary and Hematology Divisions, Department of Medicine, Foothills Provincial Hospital, University of Calgary Faculty of Medicine, Calgary.

Reprint requests to Stephen K. Field, MD, FRCP(C), Foothills Hospital, 1403 - 29th St NW, Calgary, Alberta T2N 2T9.

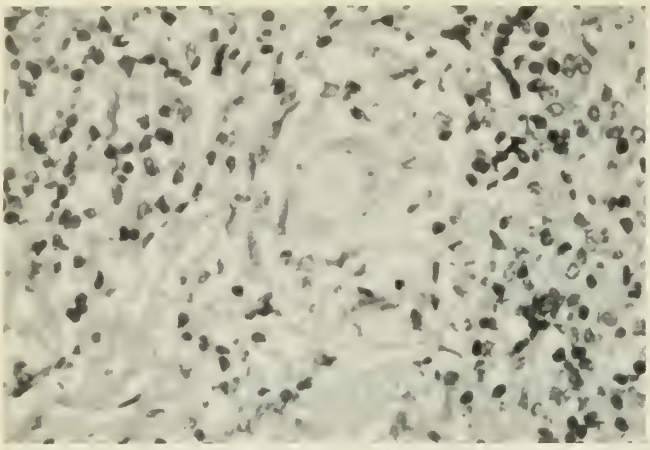


**Figure 1.**—The photomicrograph of the splenectomy specimen shows a noncaseating granuloma (original magnification × 200).

A course of prednisone, 80 mg per day, was started, and the platelet count increased to 152 × $10^9$ per liter over the following week. Four weeks later, as the corticosteroid dosage was being reduced, thrombocytopenia recurred. The patient, therefore, underwent splenectomy. After the operation, the platelet count increased to normal, allowing discontinuation of the prednisone therapy.

The spleen weighed 264 grams and contained typical noncaseating granulomata with hyalinization, consistent with a diagnosis of sarcoidosis (Figure 1). The red pulp contained foamy macrophages indicating platelet destruction. Mycobacterial and fungal stains and cultures were negative.

### Discussion

Dickerman and co-workers reported 35 cases of thrombocytopenia associated with sarcoidosis.[1] The cases were divided into three groups by the severity of thrombocytopenia and type of bleeding. Group I comprised ten patients with a high frequency of bleeding due to esophageal varices and pancytopenia including moderate thrombocytopenia. Their platelet counts returned to normal following splenectomy, suggesting that congestive hypersplenism was the responsible mechanism. Six patients had chronic thrombocytopenia with mild to moderate bleeding episodes involving skin, mucous membranes, gingiva and genitourinary tract, usually over a long period of time. All had moderate to severe thrombocytopenia. Splenectomy resulted in clinical improvement in four patients. The remaining 19 patients had severe thrombocytopenia with an acute episode of bleeding involving many sites. Five died of intracerebral bleeding. The eight patients who underwent a splenectomy recovered. Seven similar cases have been reported since 1972,[2,3,5-9] one patient dying of intracerebral bleeding.[6]

Our patient best fits the second group. He had isolated thrombocytopenia for 6½ years with only infrequent minor bleeding episodes before the recent diagnosis of sarcoidosis. He required splenectomy to control his thrombocytopenia.

The results of platelet-associated IgG assays have been reported in four thrombocytopenic patients with sarcoidosis.[2-4,9] It was reported to be weakly positive in one case, but the titer and the assay used were not reported.[3] In another case,[2] the platelets were treated with paraformaldehyde, which may result in falsely elevated values.[10] The assay was reported to be positive in one other case, but the details of that case were not included in the report.[4] The assay was negative in one other patient.[9]

The presence of increased platelet-associated IgG, megakaryocytic hyperplasia and a good response to corticosteroid therapy and splenectomy suggest that the thrombocytopenia was due to immune destruction in this patient.

Whether sarcoidosis and thrombocytopenia are causally related or coincidental events is unclear, in spite of the mentioned case reports. A systematic survey of the incidence of thrombocytopenia in sarcoidosis will be required to determine whether this association exists or not.

#### REFERENCES

1. Dickerman JD, Holbrook PR, Zinkham WH: Etiology and therapy of thrombocytopenia associated with sarcoidosis. J Pediatr 1972; 81:758-764

2. Thomas LLM, Alberts C, Pegels JG, et al: Sarcoidosis associated with autoimmune thrombocytopenia and selective IgA deficiency. Scand J Haematol 1982 28:357-359

3. Semple P: Thrombocytopenia, haemolytic anaemia, and sarcoidosis. Br Med J 1975; 4:440-441

4. Morse BS, Giuliani D, Nussbaum M: Quantitation of platelet-associated IgG by radial immunodiffusion. Blood 1981; 57:809-811

5. Case 39—1978. Case records of the Massachusetts General Hospital. N Engl J Med 1978; 299:765-769

6. Knodel AR, Beekman JF: Severe thrombocytopenia and sarcoidosis. JAMA 1980; 243:258-259

7. Weitberg AB, Passero MA: Thrombocytopenia and pulmonary hemorrhage in sarcoidosis. South Med J 1981; 74:253-254

8. James JM, Gacouin JC, Sauvaget J, et al: Sarcoïdose avec thrombopénie périphérique aiguë sévère. Nouv Presse Med 1981; 10:3853

9. Kremer H, Schuchard J, Zönnchen B, et al: Extreme thromboxytopenie bei sarkoidose. Munch Med Wochenschr 1975; 117:1479-1482

10. McMillan R: Chronic idiopathic thrombocytopenic purpura. N Engl J Med 1981; 304:1135-1147

# Atypical Diffuse Angiosarcoma of the Liver

GARY C. KANEL, MD
JACOB KORULA, MD
CHOONG T. LIEW, MD
ROBERT L. PETERS, MD†
*Los Angeles*

ANGIOSARCOMA is the most common primary malignant mesenchymal tumor of the liver; yet, its incidence is exceptionally low, ranging from 0.002% to 0.013% in autopsy series.[1,2] Only two prior cases in 96,000 autopsies have been encountered at Los Angeles County-University of Southern California (USC) Medical Center. Hepatocellular carcinoma is 30 to 81 times more frequent[2]; because angiosarcoma usually presents with signs and symptoms of chronic liver disease and initial workup often shows evidence of hepatic masses, hepatocellular carcinoma is commonly considered. Peritoneoscopy may confirm the presence of single or multiple hepatic lesions that are usually hemorrhagic, and open liver biopsy most often leads to a correct diagnosis.[3]

To our knowledge, this is the first report of a case of

(Kanel GC, Korula J, Liew CT, et al: Atypical diffuse angiosarcoma of the liver. West J Med 1987 Apr; 146:482-485)

From the University of Southern California Liver Unit, Department of Pathology, Rancho Los Amigos Medical Center, Downey, California (Drs Kanel, Korula, Liew and Peters), and the Departments of Clinical Pathology (Dr Kanel) and Clinical Medicine (Dr Korula), University of Southern California School of Medicine, Los Angeles.

†Deceased.

Reprint requests to Gary C. Kanel, MD, USC Liver Unit, Department of Pathology, Rancho Los Amigos Medical Center, 1200 Bldg, 7705 Golondrinas St, Downey, CA 90242.

ABBREVIATIONS USED IN TEXT
CEA = carcinoembryonic antigen
CT = computed tomography
USC = University of Southern California

angiosarcoma of the liver uniformly and diffusely involving all aspects of all lobes. The tumor was not diagnosed antemortem despite extensive investigation, in large part because this type of hepatic lesion had not previously been described. The diagnosis was open to question even at autopsy, confirmed only after morphologic, immunohistochemical and electron-microscopic examination.

## Report of a Case

The patient, a 37-year-old computer engineer, was referred to the USC Liver Unit at Rancho Los Amigos Medical Center with a history of jaundice and a 7-kg (15-lb) progressive weight loss for two months and peripheral edema for two weeks. He was well until one year previously, when he was noted to have gastroesophageal reflux and esophagitis at endoscopy, for which treatment with metoclopramide hydrochloride was prescribed. No varices were seen. There was no history of jaundice, alcohol excess, intravenous drug abuse, transfusions, homosexuality or long-term use of anabolic steroids or other medications. Family history was negative for liver disease. There was no exposure to toxins such as vinyl chloride, arsenicals or thorotrast (colloidal preparation of thorium dioxide); his occupation did not involve exposure to other chemicals.

On physical examination he had recent muscle wasting, multiple spider angiomas over the chest and arms, peripheral pitting edema, deep jaundice and a palpable, firm liver extending 5 cm below the costal margin at the epigastrium and 3 cm at the midclavicular line. Minimal ascites was present, and distended abdominal wall veins were noted; no bruits were heard over the liver. Abnormal laboratory test results included the following: serum albumin level 26 and globulin 29 grams per liter; alkaline phosphatase 320 (normal < 104), serum aspartate aminotransferase 52 (normal < 34) and alanine aminotransferase 24 units per liter (normal < 34), total serum bilirubin level 622.4 μmol per liter (normal <20.5), with direct bilirubin 432.6 μmol per liter, and prothrombin activity 60%. Hepatitis B surface antigen and α-fetoprotein were undetectable. Carcinoembryonic antigen value (CEA) was 33 μg per liter (normal < 5.0). The complete blood and platelet counts were normal.

Investigations before referral showed a normal liver with a large caudate lobe on computed tomographic (CT) scan and a normal transhepatic cholangiogram. A needle biopsy specimen showed pronounced sinusoidal dilatation and congestion. Hepatic vein catheterization done to exclude a venous outflow obstruction (Budd-Chiari syndrome) showed patent hepatic veins with an abnormal sinusoidal opacification. After transfer to the Liver Unit, a technetium Tc 99m sulfur colloid liver-spleen scan showed diffuse hepatomegaly with substantial redistribution without focal defects. At peritoneoscopy, the liver appeared red-black with turgid, large, irregular nodularity and increased superficial vascularity; many collateral veins were present on the falciform ligament and peritoneum. A liver biopsy specimen showed pronounced sinusoidal dilatation and rare atypical cells within the sinusoidal regions. The biopsy was not accompanied by excessive bleeding. His condition deteriorated subsequently, with the total bilirubin level rising to 778 μmol per liter and prothrombin activity falling to 38%. Progressive renal failure and encephalopathy developed, and he died of massive gastrointestinal bleeding four weeks after referral to the Liver Unit.

## Autopsy Findings

A postmortem examination was done 2½ hours after death. The liver was hypertrophic (3,050 grams) and uniformly deep red-purple. Glisson's capsule contained multiple thin fibrous septa on the surface of both the right and left lobes, giving a slightly nodular appearance. On cut section the parenchyma was uniformly hemorrhagic and spongiform, with diffuse involvement of all aspects of all lobes (Figures 1 and 2). The poorly defined cystic spaces of the spongy parenchyma ranged from pinpoint to 3 mm in diameter and were filled with unclotted blood. Only an occasional cystic space was larger, these larger spaces predominantly subcapsular and never greater than 1 cm in diameter. No nodules were

**Figure 1.**—The photograph of the gross liver specimen shows the external and cut surfaces of the hepatic angiosarcoma, with superficial nodularity but uniformity and absence of masses within the parenchyma.

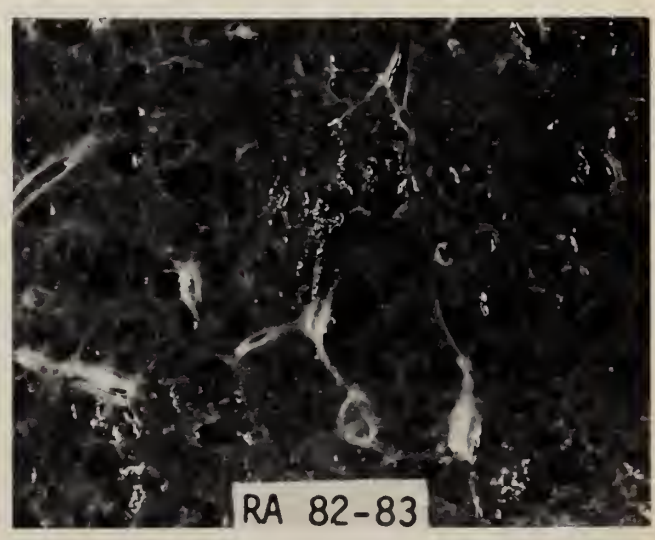



**Figure 2.**—Hepatic angiosarcoma is shown, with a hemorrhagic and spongiform pattern throughout all aspects of all lobes, the cysts pinpoint to 3mm in diameter.

present. Recognizable parenchyma was peripherally located around the cysts and was dark red-green. The subcapsular fibrous septa extended into the underlying parenchyma no deeper than 3 mm, with no subcapsular nodule formation.

Other pertinent findings included 2+ esophageal varices and 1,000 ml of bright red blood within the stomach, variceal bleeding being the immediate cause of death. The abdominal cavity contained 2.7 liters of clear yellow ascitic fluid, with no blood or blood clot formation. The spleen was slightly enlarged (260 grams). Lymphadenopathy was not present, and there was no evidence of a neoplasm in other organ systems.

The liver showed various patterns of morphologic change. Sinusoids were greatly dilated, often merging into cystic and cavernous regions. Hyperplasia and hypertrophy of the sinusoidal lining cells were prominent. Variable degrees of hepatocellular atrophy, with an increase in perisinusoidal reticulum and collagen, were present in these cords. This change often led to total disappearance of the liver cells, with their complete replacement by collagen.

Adjacent to the cystic regions, the sinusoids remained dilated, but showed a striking increase and atypicality of the lining cells, which often became multilayered (Figure 3). The cells were oval to fusiform, contained enlarged, hyperchromatic nuclei (Figure 4) and often formed solid regions containing abundant numbers of anaplastic cells. Mitotic figures and bizarre, multinucleated cells were present but infrequent. Small vascular channels composed of tumor cells were present in sinusoids and solid foci.

There was considerable cholestasis in the parenchyma least involved by tumor. The sinusoids contained varying numbers of inflammatory cells, predominantly macrophages and neutrophils. Rare foci of extramedullary hematopoiesis, a change sometimes seen in hepatic angiosarcomas, were present. There were also scattered, single, greatly hyperchromatic tumor cells within these regions. Tumor was not present in tissue sections of other organs.

A number of different antigens were stained by the immunoperoxidase technique. Factor VIII-related antigen showed focally but intensely positive intracytoplasmic granules in both the hyperplastic sinusoidal lining cells and the distinctly malignant tumor cells (Figure 5). There was strong CEA staining in bile canaliculi, but not in the cytoplasm of liver cells. There was no staining of tumor cells for CEA or $\alpha$-fetoprotein. Fibrinogen was minimally present along the pericollagenous sinusoidal borders, but was not intracytoplasmic. Staining for albumin and prealbumin was negative.

Electron microscopy showed pertinent general features. There was an increase in considerably atypical sinusoidal lining cells exhibiting irregularity in nuclear size and shape, often containing prominent nucleoli. Chromatin tended to be condensed toward the nuclear border. Intracellular organelles were scanty. No Weibel-Palade bodies, distinctive for endothelial cells, or secretory material was present. Where tumor cells were particularly numerous within fibrous regions or dilated sinusoids, new small neoplastic vascular channels, sometimes containing erythrocytes (Figure 6), were present. There was no suggestion of an epithelial origin for these tumor cells.

## Discussion

Although angiosarcoma is a very rare hepatic neoplasm, enough data have been accumulated over the years to show its

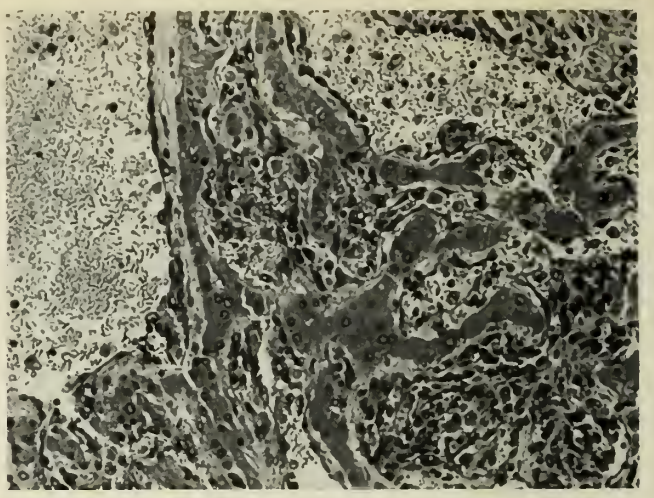


**Figure 3.**—The photomicrograph shows hepatic angiosarcoma, with pronounced dilatation of sinusoids, endothelial hyperplasia and proliferation of multilayered tumor cells. Moderate hepatocellular atrophy is present (hematoxylin and eosin stain × 255).

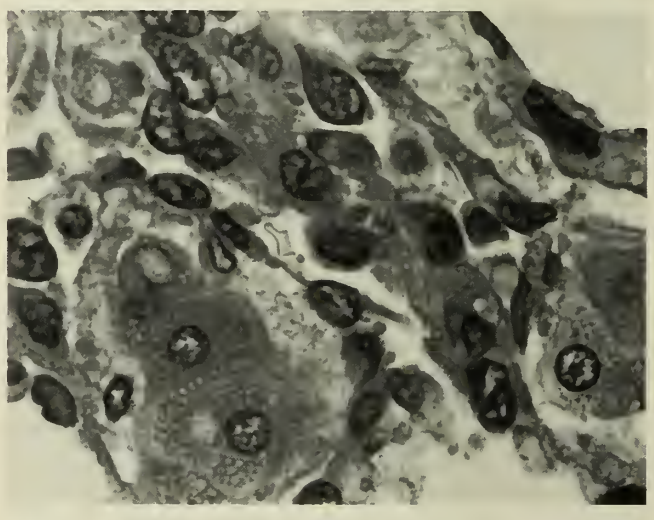


**Figure 4.**—The photomicrograph shows hepatic angiosarcoma, with enlarged, hyperchromatic tumor cells. The foamy cytoplasm in adjacent hepatocytes stained positively for fat (hematoxylin and eosin stain × 1,594).

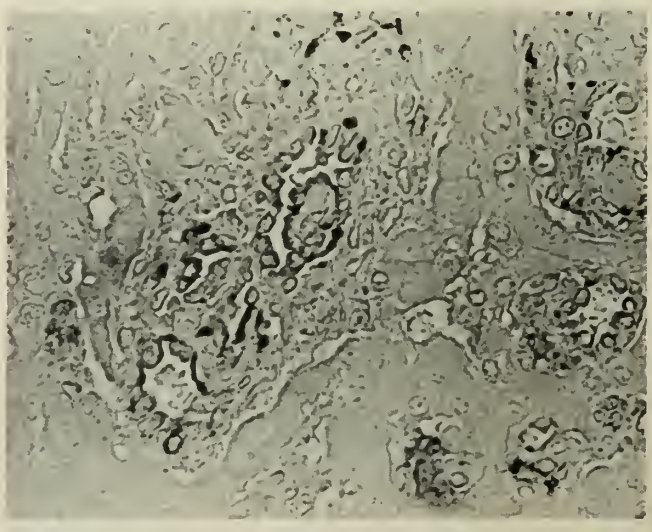


**Figure 5.**—Dark brown granular cytoplasmic staining is present in tumor cells, representing the presence of factor VIII-related antigen (immunoperoxidase stain × 680).

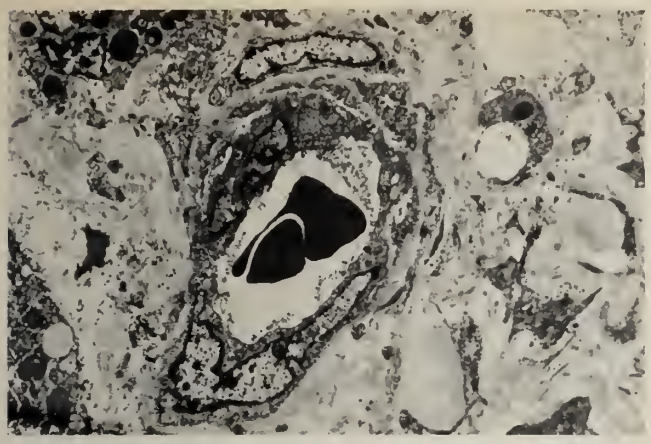


**Figure 6.**—The electron micrograph shows a dilated sinusoid containing a small vascular channel formed by tumor cells, partially surrounded by collagen fibers ( × 3,600).

distinct association in humans with long-term exposure to numerous substances such as thorotrast, vinyl chloride and arsenicals.[3] Reports of the tumor have also been documented with long-term usage of oral contraceptives,[4] diethylstilbestrol,[5] androgenic-anabolic steroids,[6] exposure to radium[7] and in patients with hemochromatosis.[8] In most cases, as represented in this report, there have been no identifiable agents or toxins.[3]

Macroscopic examination of these tumors characteristically shows many hemorrhagic nodules that usually involve both lobes. The nodules may range from pinpoint to several centimeters in diameter. Large single masses are unusual. Cut sections show the nodules to be cavernous and cystic, filled with blood or gray-white with hemorrhagic borders. Larger hemorrhagic nodules may show spongiform changes.[1]

Our patient presented with features of advanced liver disease, portal hypertension and hepatic failure. His platelets were normal and disseminated intravascular coagulation was not present. The absence of specific defects on liver-spleen and CT scans was misleading, suggesting only chronic liver disease. The bizarre gross appearance at peritoneoscopy did not suggest the diagnosis, except that a diffuse process was evident. Angiography would have been revealing but was not done because of a rapid deterioration in the patient's condition. Two uncomplicated percutaneous liver biopsies did not disclose the tumor; the macroscopic appearance at autopsy, with the spongiform change uniformly and diffusely affecting all lobes, made the diagnosis difficult initially.

The liver did, however, show morphologic and electron-microscopic features of an angiosarcoma. The confirming piece of evidence indicating the vascular endothelial origin of the neoplasm was factor VIII-related antigen in the cytoplasm of the cells. This protein is normally present in endothelial cells, megakaryocytes and platelets, and is commonly used as a marker for tumors of vascular origin.[9] Although the antigen has recently been described in squamous cell carcinoma, transitional cell carcinoma with squamous differentiation and renal cell carcinoma,[10] there was no suggestion of any of these neoplasms in this patient.

In conclusion, although morphologic examination of the liver at autopsy showed changes typical for primary angiosarcoma, the clinical and pathologic diagnostic difficulties centered around the unusual macroscopic features of the tumor. This is the first report of a case of hepatic angiosarcoma with massive and uniform involvement of the entire liver.

#### REFERENCES

1. Edmondson HA, Peters RL: Neoplasms of the liver, chap 29, *In* Schiff L, Schiff ER (Eds): Diseases of the Liver, 5th Ed. Philadelphia, JB Lippincott, 1982, pp 1137-1138

2. Ishak KG: Mesenchymal tumors of the liver, chap 12, *In* Okuda K, Peters RL (Eds): Hepatocellular Carcinoma. New York, John Wiley & Sons, 1976, pp 286-298

3. Locker GY, Doroshow JH, Zwelling LA, et al: The clinical features of hepatic angiosarcoma: A report of four cases and a review of the English literature. Medicine (Baltimore) 1979; 58:48-64

4. Monroe PS, Riddell RH, Siegler M, et al: Hepatic angiosarcoma: Possible relationship to long-term oral contraceptive ingestion. JAMA 1981; 246:64-65

5. Hoch-Ligeti C: Angiosarcoma of the liver associated with diethylstilbestrol. JAMA 1978; 240:1510-1511

6. Falk H, Thomas LB, Popper H, et al: Hepatic angiosarcoma associated with androgenic-anabolic steroids. Lancet 1979; 2:1120-1123

7. Ross JM: A case illustrating the effects of prolonged action of radium. J Pathol Bacteriol 1932; 35:899-912

8. Sussman EB, Nydick I, Gray GF: Hemangioendothelial sarcoma of liver and hemochromatosis. Arch Pathol 1974; 97:39-42

9. Sehested M, Hou-Jensen K: Factor VIII related antigen as an endothelial cell marker in benign and malignant diseases. Virchows Arch [Pathol Anat] 1981; 391:217-225

10. Wilson AJ: Factor VIII-related antigen staining by immunoperoxidase technic in smaller laboratories: A potential problem. Am J Clin Pathol 1984; 81:117-120

# Correspondence

## Addendum to Living Will

To the Editor: As our population becomes increasingly older, and our ability to keep people alive improves long after quality of life has deteriorated, one of the major dilemmas that we encounter is when to withhold life-prolonging treatment. Persons who are mentally competent can participate in the decision. The currently accepted doctrine of self-determination allows us to abide by the patient's wishes with few ethical or legal conflicts.

When the person is mentally incompetent and has not specified previously his or her wishes, however, we generally are obligated to apply all reasonable treatment to prolong life. Nursing homes in America are full of patients with Alzheimer's or other types of dementia with no hope of recovery. These persons are unable to participate in treatment decisions. Even if such a person has executed a living will, that document does not prevent interventions including hospital admission, surgical procedures, antibiotic administration, parenteral and gastric feedings for intervening medical and surgical complications and illnesses unless the person can be considered terminally ill.

In discussing this situation with my patients, friends and several groups of senior citizens, I find that nearly all persons express a desire not to have these life-prolonging measures done for them when permanent dementia or irreversible and progressive mental incompetence becomes their lot. Most persons erroneously believe that by execution of a "living will" they are protected in that situation.

To cover nonterminal situations, I have written an addendum to my living will (Figure 1). A number of friends and patients have requested a copy and have executed similar documents for themselves.

It is apparent that the American judicial system recognizes and protects the individual's right to determine his or her health care and management. Such a document explicitly defines the person's desires for the future care if mental incompetence intervenes. The family and physicians and other health care providers and institutions are specifically instructed and are therefore protected from legal liability for wrongful death when withholding life-prolonging measures. I believe that all adults should be apprised of this problem and should be offered the opportunity to make an addendum to their own living will.

W. A. REYNOLDS, MD
*Assistant Medical Professor*
*University of Washington, WAMI*
*The Western Montana Clinic*
*515 West Front St*
*Missoula, MT 59802*

ADDENDUM TO LIVING WILL
OF

_____

The following are directions to my family, my physicians and the health care institutions where I may happen to be in the event that I am not able to make valid decisions about my future care.

If and when I am no longer mentally competent and there is little or no likelihood that I will regain mental competence as determined by my physicians, I not only request but demand that the following instructions for my care be followed:

1. If I am no longer able to eat in a normal manner, I do not wish to have my life prolonged by intravenous feedings and fluids, nor nasogastric, nor other gastric feedings. It is my wish to die if nutrition cannot be provided in the normal manner.

2. In the event of infections, including pneumonia or other serious infections, I do not want parenteral antibiotics or oral antibiotics which in any way could be interpreted as life-saving. If treatment will make nursing care easier, or if needed to prevent the spread of contagious infection, then appropriate treatment can be given. Urinary tract infections can be treated only by the oral route; I refuse any parenteral antibiotics. Topical treatments can be provided to improve nursing care.

I wish to reemphasize that when I am no longer mentally competent, it is my wish to die in a normal course of events without benefit of medical intervention. If I am at home and can be taken care of there, I do not wish to be taken to a hospital for specific treatment, except in the case when nursing care is required that cannot be provided at home. If I am in a nursing home and become ill, I do not wish to be transferred to a hospital, the only exception being when it is impossible to provide the nursing care in the nursing home. Specifically, I refuse permission to be transferred to the hospital if the purpose is to prolong my life.

_____ DATE _____ SIGNED

_____ WITNESS

_____ WITNESS

**Figure 1.**—Sample of "Addendum to Living Will" used by author.

## Cost-Effectiveness of Fecal Occult Blood Screening

To the Editor: The recent review of fecal occult blood screening (FOBS) by Brendler and Tolle[1] summarizes the current mainstream thoughts on colon cancer screening as supported by the American Cancer Society.[2] A closer evaluation of FOBS is warranted because much of the rationale is not well developed.

The FOBS is plagued with a low predictive value positive. Though FOBS carries a 1% to 2% false positive rate,[2,3] the article correctly notes that only about 50% of the positive tests are true positive for neoplasia; of the positives about 10% are cancer and about 40% are polyps. While at first glance this 50% predictive value may appear acceptable, a closer analysis is required because only 5% to 10% of polyps will ever become cancer and then probably at least five years in the future.[4] Screening, therefore, actually finds 10% cancer and 2% polyps that will become cancers for a total of 12% life-threatening lesions. The 1% to 2% false positive rate thus correlates with a 12% predictive value positive, indicating the vast majority of those screening positive will undergo the extensive, expensive and potentially dangerous workup needlessly. It has been estimated that if FOBS were applied to the entire American population age 45 and above, the ensuing evaluation of all people with positive results would lead to about 3,000 "serious illnesses" (bowel perforation, sepsis and the like) and 100 fatalities annually.[5] The majority of these unfortunate people would be free of neoplasia.

The article also indicates a lack of sensitivity (that is, a large false negative rate) with FOBS. FOBS misses about 75% of the polyps and about 25% of the cancers found by flexible sigmoidoscopy.[6] Given that only half of cancers and polyps are within the reach of the sigmoidoscope, the actual

number missed in the whole colon is approximately twice these numbers. Thus a large portion of people with disease are falsely reassured; indeed the number falsely reassured exceeds the number of true positives.

Although FOBS will clearly detect some colorectal cancers and precancerous polyps, it cannot be considered an inexpensive procedure. In fact, one study has shown FOBS to be less than one-twentieth as cost effective as flexible sigmoidoscopy (Anderson JP, Ganiats TG, Kazemi MM: Screening and treatment for colorectal cancer: A benefit-cost/utility comparison of flexible sigmoidoscopy and fecal occult blood methods using the General Health Policy Model, unpublished data). Unfortunately, enthusiasm for FOBS has not awaited a reevaluation of its cost effectiveness, and over-the-counter FOBS interventions done without medical supervision are likely to muddy the waters further. In this age of cost-containment it is incumbent upon the public and the medical community to reevaluate the cost effectiveness of fecal occult blood screening for colon cancer.

THEODORE G. GANIATS, MD
*Assistant Clinical Professor*
WILLIAM A. NORCROSS, MD
*Associate Clinical Professor*
*Division of Family Medicine*
*University of California, San Diego, School of Medicine*
*La Jolla, CA 92093*

REFERENCES

1. Brendler SJ, Tolle SW: Fecal occult blood screening and evaluation for a positive test. West J Med 1987; 146:103-105
2. American Cancer Society: Guidelines for the cancer-related checkup: Recommendations and rationale. CA 1980; 30:194-240
3. Eddy DM: Screening for cancer: Theory, analysis and design. Engelwood Cliffs, NJ, Prentice-Hall, 1980
4. Day DW, Morson BC: The adenoma-carcinoma sequence, Chap 6, *In* Morson BC (Ed): The Pathogenesis of Colorectal Cancer. Philadelphia, WB Saunders Co, 1978, pp 58-71
5. Frank JW: Occult blood screening for colorectal carcinoma: The risks. Am J Prev Med 1985; 1(4):25-32
6. Simon JB: Occult blood screening for colorectal carcinoma: A review. Gastroenterology 1985; 88:820-837

## Was It Worth It?

To the Editor: This is in response to your editorial "$250,000—Was It Worth It?" in the January issue.[1] In the case report you discuss,[2] a habitual intravenous drug abuser survived nine admissions for mitral valve endocarditis, including two valve replacements, accumulating more than one hospital-year out of the past 12 years. Was spending all that money on this loser worth it? Did other people, more deserving of health care, not get it because of him?

I wonder how much of your skepticism stems from moral considerations about this patient's worth to society. I have trouble imagining that you would make a similar remark about a case report of a housewife with an exceptional case of systemic lupus, who survives repeated hospital stays and runs up a huge bill that society must pay.

I confess that I do not feel entirely sanguine about cases like this either. I pay taxes too, and thank goodness that there are not more patients like this fellow than there are. I believe, however, that we must resist firmly any effort to put us medical doctors in the position of judging who is fit to be treated, and who is condemned to be declared surplus. I have seen scenarios like that in Orwellian science fiction stories.

When I am faced with moral dilemmas such as are exemplified by this case, I remember a quotation from Mencken: "The purpose of the medical profession is not to make men virtuous. It is to rescue them from the consequences of their vices."

I emphasize that I am addressing the idea of whether to decide to treat on the basis of the patient's moral worth. I do not advocate futile treatment that needlessly prolongs suffering.

RICHARD M. COHEN, MD
*Fong Diagnostic Laboratory*
*7224 Florin Mall Drive*
*Sacramento, CA 95823*

REFERENCES

1. Watts MSM: $250,000—Was it worth it? (Editorial). West J Med 1987 Jan; 146:86
2. Simonson J, Schaaf VM, Mills J: Nine episodes of infective endocarditis in one patient—A new record. West J Med 1987 Jan; 146:96-98

* * *

To the Editor: I read your editorial in the January 1987 issue: "$250,000.00—Was It Worth It?"[1] I do not believe it was worth it.

An individual has a right to do anything to his body he cares to do. However, when a physical abuse that is self-inflicted becomes a financial burden on me (society), then that right ceases. We all know that in all aspects of our lives we can do anything we care to do as long as we do not violate the rights of others. When a person abuses his body, that is his right. When he abuses it to the point of seeking health care and I am financially responsible, then he violates my rights.

The answer to your question—"Was It Worth It?"—is no. In instances of physical abuse that is self-inflicted where there is no financial responsibility, the individual person seeking treatment should simply be given a comfortable place in the hospital where the person is maintained, and if he survives, he survives. If he does not, he does not. This would save vast sums of money spent on a hopeless problem, allowing the expenditure of the same money in needed areas. For those who are financially responsible—for instance, with medical insurance—there should be surcharges to cover the added costs incurred by their physical self-abuse. I note that some insurance companies are already headed in that direction, giving discounts for nonsmokers and nondrinkers.

The problems of physical self-abuse will always be with us. The financial responsibility for that abuse should be placed squarely on the person abusing himself. Just possibly not spending the money on those who do abuse themselves would reduce their numbers so that others who really need health care would have funds available.

GLENN W. DRUMHELLER, DO
*1515 Pacific Avenue*
*Everett, WA 98201*

REFERENCE

1. Watts MSM: $250,000—Was it worth it? (Editorial). West J Med 1987 Jan; 146:86

## Natural Death Acts

To the Editor: I am writing regarding the Commentary "Nora's 'Living Will' " by Dr E.R.W. Fox in the January issue.[1] It was sensational!

We here in the state of Washington are wrestling with revisions of a "natural death act" that, we hope, ought to be adopted this year. Moreover, the Washington State Medical Association has agreed to "push" discussion time about living wills and death and dying with patients so that the issue

"escapes from the closet." Dr Fox's capsulization of his quandary should certainly help broaden the understanding of the issues involved.

WILLIAM O. ROBERTSON, MD
*Children's Orthopedic Hospital and Medical Center*
*4800 Sand Point Way NE*
*Seattle, WA 98105*

REFERENCE

1. Fox ERW: Nora's 'living will.' West J Med 1987 Jan; 146:118

## Cognitive-Procedural Differences

To the Editor: The letter[1] by Stephen D. Leonard, MD, on the concept of cognitive versus procedural care that was published in the February 1987 issue is as remarkable for its prejudice as it is for its ignorance.

The American Society of Internal Medicine and others have unceasingly pointed out that *all* physicians do cognitive work. The question is not that one kind of physician is smarter than the next, but rather that remuneration is so unequal when procedural and nonprocedural services are rendered. This has led to an increasing disparity in income between the primary care and other branches of medicine.

Attempts to adjust cognitive-procedural differences are really an attempt to *avoid* a war among the branches of medicine by making adjustments that bring remuneration more into line with the resource cost of producing medical services.

There may possibly be a better way of labeling the problem than calling it "cognitive-procedural," but to treat it with contempt is to virtually say "Let them eat cake." Who is it, then, who is trying to produce discord within the house of medicine?

PHILIP R. ALPER, MD
*1838 El Camino Real, Suite 102*
*Burlingame, CA 94010*

REFERENCE

1. Leonard SD: Concept of cognitive versus procedural (Correspondence). West J Med 1987 Feb; 146:235

## Illness From Organophosphate Exposure

To the Editor: The comparison of cholinesterase values before and after oxime administration, suggested by Izraeli and co-workers,[1] is a clever approach to the confirmation of organophosphate-induced pesticide illness in the absence of preexposure cholinesterase values.

This method will not work in all cases, however.

Persons who become ill after exposure to organophosphates may receive pralidoxime without any substantial effect on their cholinesterase levels, if they have had chronic exposure to these pesticides. This would result from preexisting but nonsymptomatic inhibition of cholinesterase activity—that is, a patient with a substantial portion of the enzyme already irreversibly bound to insecticide.

Neither this method, nor the method we have described,[2] overcomes the limitations of the cholinesterase analysis, which preclude it from being the means of excluding the diagnosis of pesticide poisoning. Carbamate insecticides cause cholinesterase inhibition and cholinergic symptoms, but such inhibition cannot be detected by a cholinesterase analysis, as the bond between enzyme and insecticide is so labile that activity is restored by the analytic procedure. We wonder whether the test may be inadequate to detect symptomatic but mild cases of organophosphate-induced illness as well.

Izraeli and co-workers have, however, provided another useful clinical tool. A minor criticism of their letter is to note that oxime therapy does not necessarily reactivate erythrocyte cholinesterase to a greater degree than plasma cholinesterase. In some cases, it is the plasma cholinesterase that has shown the greater reactivation.[3] This is not surprising in that some pesticides inhibit plasma cholinesterase more dramatically than the erythrocyte enzyme.[4]

ANTONIO R. VELASCO, MD
PAUL G. BARNETT
JOHN E. MIDTLING, MD, MS
*Family Practice Residency*
*Natividad Medical Center*
*PO Box 81611*
*Salinas, CA 93912*

REFERENCES

1. Izraeli S, Glikson M, Ziv I: Diagnosis of organophosphate poisoning (Correspondence). West J Med 1986; 145:698

2. Midtling JE, Barnett PG, Coye MJ, et al: Clinical management of field worker organophosphate poisoning. West J Med 1985; 142:514-518

3. Quinby GE: Further therapeutic experience with pralidoximes in organic phosphorous poisoning. JAMA 1964; 187:114-118

4. Hayes WJ: Pesticides studied in man. Baltimore, Williams & Wilkins, 1982, p 309

## Educating the Public About Life-Style and Nutritional Practices

To the Editor: I would like to make some comments regarding the article in the Forum section entitled "Educate, Educate, Educate" by R. W. Odell, Jr, MD.[1] I heartily agree with Dr Odell that the funding of our health care is forcing a long needed reappraisal of values we as physicians have taken for granted. I also agree that a competent physician educates his or her patients as part of his or her treatment. He states, "American medicine will regain its preeminence in our society only in so far as it reassumes this vital function of educator about matters medical. This will require brutal honesty and much soul searching, for past deficiencies are not easily made up."

I would differ with him, however, on where the emphasis should be on education. All of the things that he points out I think are valid. However, we as physicians must come to the realization that the great majority of our major illnesses are largely self-inflicted by self-destructive life-style and dietary habits. They are, therefore, largely preventable. Our emphasis in medicine has been largely on diagnosis and treatment of established disease. As long as we continue to place the emphasis on ever more sophisticated means of diagnosing and treating diseases, we are only going to drive up the cost of health care. We must find a means of reducing the supply of sick patients. Even the National Cancer Institute has acknowledged that we do not need a single new breakthrough in diagnosis or treatment. If we could just put into practice what we already know about diagnosing and treating disease, and particularly what we know about preventing cancer, and the same may be said of cardiovascular disease, we could greatly reduce the death rate from cancer by the turn of the century. We have already seen a significant reduction in age-adjusted death rates from coronary artery disease as the public has become aware of the relationship of smoking, diet and exercise to cardiovascular disease. Currently in the United States, nearly one half of all people succumb to a single disease process, namely, atherosclerosis, the underlying cause of most heart attacks and strokes. We certainly have sufficient evidence now to realize that atherosclerosis can certainly be minimized if not eliminated by appropriate life-style and dietary practices.

It has been my experience that appropriate life-style and dietary practices are much more effective in preventing disease and promoting wellness than in restoring health once you have lost it. And, I might add, it is much less expensive to prevent disease than to restore health.

So I agree with Dr Odell that we must educate, educate, educate. But I believe that the emphasis must be on getting appropriate mass media information to the public, emphasizing that they are largely responsible for their own health by choosing appropriate life-style and nutritional practices.

IRA E. BAILIE, MD
*Turlock Medical Clinic*
*1015 E Main St*
*Turlock, CA 95380*

**REFERENCE**

1. Odell RW, Jr: Educate, educate, educate, *In* The Aim of American medicine within the constraints of today's society—A forum. West J Med 1987 Jan; 146:107-108

## Healing the Healers

To the Editor: Medicine is being buffeted by gale force winds of change. DRGs are challenging old habits and causing tremendous shifts from inpatient to outpatient oriented care. Traditional fee-for-service medicine is giving way in some areas to corporate for-profit medical systems. The increasing number of physicians in all specialties is raising competitive fears.

Physicians are frustrated, angry and afraid. Frustrated for feeling that these changes aren't all positive and are out of their control; angry, because even survival of the best aspects of our medical care are threatened and afraid because their role of patient advocate is being challenged, given the current new constraints.

The public continues to hold a negative image of our profession as arrogant, self-serving and greedy. I am worried that to an extent this perception is accurate. Ultimately, our profession will be judged by how we take care of our patients and how well we take care of each other. Increasingly we are seeing evidence of lack of cooperation within our own profession. Turf battles are rife as the number of physicians in various specialties increases. The doctor glut has us tripping over one another to market our products. Some specialties are increasingly reluctant to teach physicians in training in other specialties for fear of worsening the competition. Some have forgotten the very core of the Hypocratic Oath. Hospital privileging is becoming blurred because of competitive factors, always under the seductive hubris of quality care. Continuing medical education activities are becoming elitist and closed to certain specialties.

If physicians can't treat others in their own profession with dignity, trust and respect, is it any wonder that the public doubts our true intent when we espouse these qualities in their care? These internecine squabbles will be used to further divide and conquer our profession by those whose only interest in medicine is the commercial ability to exploit it. We must use the glue of cooperation to heal these wounds in our own profession. Our specialty organizations must be leaders in this effort. Only when we begin healing ourselves by showing mutual trust, respect and dignity toward one another will we be successful in healing our image in the eyes of the public.

JOHN J. MOHR, MD
*Director*
*Family Practice Residency of Idaho, Inc*
*777 N Raymond St*
*Boise, ID 83704*

## Correction: Common AIDS-Related Problems

To the Editor: In reading the article "Practical Management of Common AIDS-Related Medical Problems"[1] by Dr Harry Hollander in the February 1987 issue, I noted what I believe is an error in Table 6 ("Causes of Diarrhea in Patients at Risk for Acquired Immunodeficiency Syndrome") on page 239. Under the section "Infectious enterocolitis," it appears that *Entamoeba histolytica* was incorrectly printed as *Escherichia histolytica*.

NANCY KURAHASHI
*Editor*
*Lange Medical Publications*
*Los Altos, CA 94023*

**REFERENCE**

1. Hollander H: Practical management of common AIDS-related medical problems. West J Med 1987 Feb; 146:237-240

Editor's Note:

Ms Kurahashi is correct. It should have been *Entamoeba histolytica*.

Topics in Primary Care Medicine

# Screening in Preventive Care for Adolescents

PAULA BRAVEMAN, MD, *and* KATHLEEN E. TOOMEY, MD, MPH, *San Francisco*

*"Topics in Primary Care Medicine" presents articles on common diagnostic or therapeutic problems encountered in primary care practice. Physicians interested in contributing to the series are encouraged to contact the series' editors.*

BERNARD LO, MD
STEPHEN J. McPHEE, MD
Series' Editors

Preventive health care has received increasing attention in the medical literature, with rational screening strategies replacing the once-valued annual physical examination. In adolescence, visits to the doctor may occur only for a school physical or an acute illness, and integration of preventive health services with medical care is especially important.

Although a time of rapid physical and psychological development, adolescence is usually free of the severe acute illnesses of childhood and debilitating chronic conditions of adulthood. Societal changes, however, including the prolongation of teen dependency, have intensified behavioral problems of the adolescent period. The major health risks for US adolescents are behavioral. Up to 76% of adolescent deaths in the United States are caused by accidents, homicide and suicide; the rate of adolescent suicide has tripled in the last 20 years. Adolescent pregnancy, sexually transmitted diseases and substance abuse, especially alcohol and cigarettes, adversely affect the health of adolescents.

A rational approach to health screening for adolescents would systematically address their most significant risks for morbidity and mortality, not only in youth but also in adulthood. Health maintenance protocols for children and for adults, organized as checklists in medical charts, are familiar to most primary care physicians. This format can be an effective way to incorporate screening into routine clinical practice with adolescents (see Figure 1).

Screening protocols generally are designed to identify persons at risk for future morbidity or to detect disease at a treatable or reversible stage. A good screening test is safe, easy to do, acceptable to patients and sensitive. An ideal test would also be inexpensive and would have few false positive results. Techniques that enhance communication between patient and provider can increase the sensitivity and specificity of screening for behaviorally-related conditions as well as the utilization by the patient of available preventive services in general.

The value of early identification of such organic conditions as high blood pressure and cervical dysplasia is well established. The literature is less developed regarding screening and intervention for behavioral problems. Studies of adolescents who have attempted suicide have shown that frequently a long series of episodes of self-destructive behavior and multiple medical visits with vague or misleading complaints have preceded the attempt. While it seems logical that early identification would alter outcome, there is no definitive proof that screening for most behavioral risks is effective. The following screening recommendations for adolescents, therefore, are based on the weight of the existing literature and the authors' judgment.

## Recommended Screening Procedures

*Complete History*

At least once during the teen years a complete medical history, including perinatal and childhood history, should be taken with a parent present at least part of the time. This may be a teenager's first opportunity to hear his or her own and family medical history. Both parent and child should be allowed to answer questions. Their interaction may be informative. It is also essential that the physician establish a routine practice of talking with the adolescent patient without the parent present for some time; the physical examination is a convenient context for confidential exchange.

The complete history can be taken initially by the nurse following a written form, without pursuing details unless encouraged. The initial history is reviewed and expanded by the physician. The physician may review the history with a parent present, focusing on sensitive areas later when alone with the patient.

Often, a first visit in which a teenager reveals little information of a private nature is followed by return visits with increasing openness. Providers should avoid probing an adolescent patient before trust has been established. An additional danger is that of inadvertently establishing an adversarial relationship with parents. Confidentiality must be addressed explicitly; for example, with a statement such as, "Now that you are a teenager, there may be some things on your mind that are very personal and private. I want you to know that we can talk about anything you want, and that I won't tell your parents unless I have your permission." A good discussion of confidentiality and legal issues in seeing

(Braveman P, Toomey KE: Screening in preventive care for adolescents. West J Med 1987 Apr; 146:490-493)

From the Division of Family and Community Medicine (Dr Braveman) and the Institute for Health Policy Studies (Drs Braveman and Toomey), University of California, San Francisco, School of Medicine.

Reprint requests to Paula Braveman, MD, Box 0900, AC-9, University of California, San Francisco, CA 94143.

adolescent patients is found in a recent article by Strasburger and co-workers.

Depression in an adolescent may require patience to uncover. The younger the teenager the more likely that vegetative signs common in the depressed adult will be absent. "Acting-out" or inability to function may indicate depression; school performance history is important. Frequent fights, accidents or substance abuse may indicate depression or anger.

Questions should be framed in concrete language; the younger teen still may not be able to abstract. The technique of beginning a question with "Some people your age . . ." before asking "Do you . . . ?" is a well-tested aid. This is a way of stating implicitly that the questioner will not be shocked or angered by an affirmative answer.

Inquiries should be made regarding exercise, diet, alcohol, cigarettes and prescription and nonprescription drugs with an attempt at quantifying. Questions related to sexual activity and substance abuse are best pursued during the examination when provider and patient are alone. The provider should not ignore the possibility of homosexual activity; relevant health issues, needs and risks will be different. A sample technique for eliciting information on contraception is, "Many young people your age are interested in learning about birth control. Do you have any questions about this?" One may ask of teens thought to be sexually active, "Are you using any kind of birth control or protection like rubbers or foam or pills or anything else?" Sexual abuse may be difficult to elicit by history; sexually transmitted disease in a young teen should raise this question.

| Procedure | Recommended Frequency | Last Known 1986 1987 etc |
|---|---|---|
| 1. Complete history | Once | |
| 2. Immunization update | See Figure 2 | |
| 3. History update | Every 1-2 years, or every 6 months where appropriate* | |
| 4. Complete physical exam | Once | |
| 5. Breasts/testes self-exam taught | Once | |
| 6. Visual acuity | Once | |
| 7. Audiology | Once for high risk | |
| 8. Dental referral | Every year | |
| 9. Tuberculin test | Every 1 to 2 years for high risk | |
| 10. Sickle screen | Once all blacks | |
| 11. Hgb or Hct | Once postpuberty for low risk | |
| 12. Urinalysis | Once | |
| 13. Cholesterol | Once if high risk | |
| 14. Pap smear | Every year where appropriate* | |
| 15. Neisseria and chlamydia screens† | Every 6 to 12 months where appropriate* | |
| 16. Serology† | Every year where appropriate* | |

Hct=hematocrit, Hgb=hemoglobin, Pap=Papanicolaou

*"Where appropriate" is code for sexually active which is not written on a face sheet because of risk of parental observation during routine visit.

†For reasons noted above (*), neither the word "gonorrhea" nor "syphilis" are written on the face sheet.

**Figure 1.**—Adolescent Health Screening Schedule

For adolescent girls, reproductive history should be sought, including menarche, gravity/parity and last menstrual period, as well as DES exposure in utero. It is worthwhile to ask the date of the last menstrual period routinely of every adolescent girl on every visit.

Interval histories should be repeated every one or two years. Sexually active adolescents should be seen at least every six months for history, contraceptive update and counseling; screening for sexually transmitted disease is indicated every 6 to 12 months.

*Complete Physical Examination*

Teenagers are often concerned about the profound body changes that accompany puberty, and many worry that they are not normal. The physical examination, alone with the physician, is a safe time for a teenager to ask questions. Questions should be encouraged and responses directed toward providing reassurance where appropriate. The complete physical examination should be done at least once during the adolescent years and for most teens will be brief compared with the history and discussion. A breast examination on young women and a testicular examination on young men can be accompanied by instructions for self-examination, introducing an important practice. The first pelvic examination can be anxiety-provoking, and requires patience and preparation. A digital examination to assess appropriate speculum size and position of cervix should precede insertion of speculum; smaller specula should be available. Draping is especially important, given an adolescent's often intense self-consciousness. Discussion of sensitive issues should be avoided while the patient is undressed and hence more vulnerable.

Every examination should include a blood pressure measurement. Measurements of height and weight should be routine, in part because of the prevalence and importance of eating disorders in this period. Certain orthopedic conditions presenting during adolescence such as Osgood-Schlatter disease, slipped femoral capital epiphysis and scoliosis may be noted with careful history and physical examination.

*Visual Acuity*

Approximately 18% of children with normal vision at age 7 will have visual defects when screened at age 16. Snellen testing is able to detect significant visual defects and should be done routinely at least once during adolescence.

*Auditory Screening*

The sensitivity and specificity of repeated auditory screening in well adolescents without related complaints or school problems has not been determined. High-risk groups, who may benefit from routine screening, include those with school difficulties or communication problems, those involved in activities with significant noise exposure (for ex-

ample, those playing in rock bands) or those whose medical history is unknown.

*Referral for Dental Screening*

Approximately 68% of youth in a large national study in the 1970s needed dental care. Dental care is correlated with socioeconomic status. Education about dental hygiene and need for referral can take place during the history and physical. Studies from Britain have shown that maximum cost benefit can be obtained from yearly dental examinations during this high-risk period. Primary care physicians should try to facilitate dental referrals at least once a year.

*Tuberculosis Screening*

The American Thoracic Society advises routine screening only for those at high risk for tuberculosis infection. Persons considered at risk include those who have had contact with a case of active tuberculosis, residents of institutions or communities where tuberculosis prevalence is suspected to be high, immigrants from high prevalence regions, Native Americans and low-income groups living or working in crowded conditions. Adolescents in these groups should be screened with a PPD (five tuberculin units) every one to two years. The specificity of the PPD is low in persons likely to have been vaccinated with bacille Calmette-Guérin (BCG). Variability, however, in efficacy of BCG vaccination dictates that all newly recognized tuberculin reactors be considered at risk for subsequent development of active disease.

*Laboratory Screening*

*Screening for anemia.* Androgen-induced red cell production in males and menstrual losses in females may lead to depleted iron stores in adolescence. The prevalence of iron-deficiency anemia in teenagers ranges from 5% to 20%, with the highest rates in low-income and black girls and in pregnant teenagers. A single screening with hemoglobin or hematocrit is recommended after puberty for low-risk teens; repeat screens are indicated for those in high-risk groups. No evidence exists for the value of a complete blood count in screening well youth.

*Sickle cell screening.* Approximately 10% of black people in the United States carry the hemoglobin S trait. Screening for sickle trait is advisable for all blacks during adolescence before reproductive decisions are made.

*Cholesterol.* Adolescents with a family history of hyperlipidemia or of early coronary artery disease may have detectable lipid abnormalities that will benefit from cholesterol-lowering interventions. A fasting cholesterol study should be done once during adolescence in this high-risk group. There is not general agreement regarding initial testing for triglyceride levels; most sources argue that isolated triglyceride abnormalities are rare and hence initial screening for cholesterol alone is rational.

*Screening for sexually transmitted diseases.* Screening of sexually active adolescents may prevent the long-term reproductive sequellae associated with the rising rate of sexually transmitted diseases in this group. Chlamydial infections have been detected in as many as 40% of teenagers on screening of selected populations. *Chlamydia trachomatis* infection is often asymptomatic and more long-term morbidity is associated with it than with *Neisseria gonorrhoeae*. Screening can be done routinely in adolescent girls at the time of the annual Pap smear. First void urinalysis in teenage boys can provide a screen for both asymptomatic chlamydial and gonococcal urethritis. Inexpensive nonculture screening tests for chlamydia, relying on swabs from the endocervix and urethra, are now available. These methods have been described by Tam and co-workers and Jones and associates.

*Papanicolaou (Pap) smear for cervical cancer.* Recent studies of sexually active adolescent girls have shown rates of cervical dysplasia or neoplasia of 37 to 70 per 1,000. The smear is highly sensitive for dysplasia of the cervix. After an initial negative screen the Pap smear may be repeated every three years. Annual visits, however, provide a convenient and routine context for surveillance of sexually transmitted diseases and contraceptive counseling.

*Urinalysis.* The low predictive value of a urinalysis in a well adolescent makes it reasonable not to repeat this procedure routinely after an initial negative screen in the teenage years. Routine screening cultures for occult bacteriuria are not indicated.

*Immunization*

*Tetanus-diphtheria* (Td) preparation is the recommended vaccine for adolescents and adults because a large proportion lack circulating diphtheria antibody. Pertussis vaccine is contraindicated after age 7. All adolescents lacking reliable history of primary tetanus and diphtheria series should complete the series following an abbreviated vaccination schedule (see Figure 2).

*Oral polio virus* should generally not be administered to previously unimmunized persons over 18 years of age because of reports of clinical disease after live virus vaccination in this age group. Inactivated polio virus vaccine is not readily available to clinicians.

An estimated 20% of young adults lack detectable measles antibody and may be susceptible. *Measles vaccine* is indicated for all adolescents who lack documentation of physician-diagnosed measles, receipt of live measles vaccine on or after

| | Date | Date | Date | etc |
|---|---|---|---|---|
| Td ×3 (at least 6 weeks apart) or Hx of DPT ×3 | | | | |
| Tetanus toxoid booster every ten years (may be given as Td) | | | | |
| Polio: OPV ×3 if less than 18 years old<br>IPV ×2 if 18 years old or over and previously unimmunized | | | | |
| Measles: Hx vaccine* after age 12 months or Hx illness | | | | |
| Mumps: Hx vaccine* or Hx illness | | | | |
| Rubella: Hx vaccine* after age 12 months (given within 10 years or positive titer) | | | | |

DPT=diphtheria, pertussis and tetanus; Hx=history of (assumes documentation); IPV=inactivated polio virus; MMR=combined measles, mumps, rubella; OPV=oral polio virus; Td=adult tetanus and diphtheria

*Alone or as MMR

**Figure 2.**—Immunization Recommendations and Schedule for Adolescents.

their first birthdays or laboratory evidence of immunity. The goal of *rubella* immunization is the prevention of congenital rubella syndrome. Children 1 to 12 years of age and postpubertal girls and women of child-bearing age found susceptible on antibody screening should be immunized to prevent congenital rubella syndrome. Although it appears that risks from inadvertent immunization in the first trimester are low, care should be taken to avoid immunization during unsuspected pregnancy. Measles as well as rubella vaccines given before age 12 months may not create lasting levels of immunity. Postpubertal boys with mumps infection have a 20% risk of orchitis that can occasionally result in sterility. *Mumps vaccine* is indicated for any adolescent, particularly boys, believed susceptible by history. Vaccination with *combined measles, mumps and rubella* vaccine of persons previously immune to one or more of its components is safe and can be used for an adolescent with uncertain infection or immunization history.

## Final Remarks

A primary care physician can effectively integrate preventive and curative measures in an office practice and should provide adolescents with counseling as well as specific disease screening. A checklist on the face sheet in a patient's chart is a convenient reminder and aid in organizing the agenda for a visit. A screening protocol for adolescents may serve the dual function of detecting age-specific risks as well as developing positive health habits that can continue to be of benefit into adulthood. Use of such a protocol can help both patient and physician move forward in a safe routine that permits assembling of valuable information and establishment of trust.

### GENERAL REFERENCES

Barnes HV (Ed): Symposium on adolescent medicine. Med Clin of North Am 1975; 59:4

Canadian Medical Task Force on the Periodic Health Examination: The periodic health examination. Can Med Assoc J 1979; 121:1193-1254

Canadian Medical Task Force on the Periodic Health Examination: The periodic health examination II. 1984 update. Can Med Assoc J 1984; 101:866-868

Canadian Task Force on Cervical Cancer Screening Programs: Cervical cancer screening programs: Summary of the 1982 Canadian task force report. Can Med Assoc J 1983; 127:581-589

Jones MF, Smith TF, Houglum AJ, et al: Detection of *Chylamdia trachomatis* in genital specimens by the chlamydiazyme. J Clin Microbiol 1984; 20:465-467

Litt IF (Ed): Symposium on adolescent medicine. Pediatric Clin North Am 1980; 27:1

Rapp CE: The adolescent patient. Ann Intern Med 1983; 99:52-60

Strasburger VC, Eisner JM, Tilson JK, et al: Teenagers, physicians, and the law in New England. J Adol Health Care 1985; 6:377-382

Tam MR, Stamm WE, Handsfield HH, et al: Culture-independence diagnosis of *chlamydia trachomatis* using monoclonal antibodies. N Engl J Med 1984; 310:1146-1150

# Physicians as Patients—The Use of Obstetric Technology in Physician Families

CARIN E. DUGOWSON, MD, MPH, *Seattle, and* STEPHEN K. HOLLAND, MD, *Lexington, Massachusetts*

*Birth records of King County, Washington, for 1980 through 1982 were reviewed to study the use of obstetric technology by physician and nonphysician families. The sample of 524 births to physician families was compared with 657 births to nonphysician families randomly selected from upper income census tracts. Though similar in demographic and medical characteristics and pregnancy outcomes, the two groups differed greatly in use of amniocentesis and cesarean section. Physician families used amniocentesis 1.65 times more often than nonphysician families and women physicians were 3 times more likely to have the procedure (relative risk [RR] 3.09). For female physicians 30 to 40 years old, the RR was 5.54. Similarly, physician rates for primary cesarean section were 1.56 times higher and rates for women physicians were twice as high as for controls (RR 2.14). This study suggests higher utilization rates among physicians for some procedures. These findings may foreshadow increases in utilization in the general population.*

(Dugowson CE, Holland SK: Physicians as patients: The use of obstetric technology in physician families. West J Med 1987 Apr; 146:494-496)

It has been estimated that physicians control up to 80% of personal health care expenditures.[1] By recommendations in clinical practice, physicians shape patterns of use of medical technologies that are often costly and potentially morbid.[2] Such recommendations necessarily depend on the physicians' medical beliefs and should be mirrored, therefore, in their own health care behavior.

Physicians as a group, in fact, epitomize informed consumers in the use of medical technology. Practical experience with various medical interventions coupled with an understanding of the costs and benefits of specific technologies should enable the physician to act in a rational and judicious manner. Relatively few studies, however, have investigated the manner in which physicians themselves use medical care. Of the surveys found in the literature, most show physicians and their families to be relatively high[3,4] but erratic users of medical intervention.[5]

This study was designed to examine the personal use by physicians of obstetric technology. This field is of interest for several reasons. Technology in this area is growing rapidly, with both new techniques available and a broadening of the indications for their use. Second, the birth of a child is an event of major importance, with much consideration given by prospective parents—physicians or not—to the use of medical intervention. Finally, changes in either health care policy or patient-generated demand with respect to the use of elective obstetric procedures could have a significant effect on health care costs.[6,7]

## Materials and Methods

Birth records for Washington State have been computerized since 1980 and include detailed occupational codes for both parents. Birth data for King County (Seattle and environs) were reviewed. All births to physicians or their spouses for 1980 to 1982 were identified by the occupation coding on the birth records (n = 587). A comparison sample of 906 King County births to nonphysician families was randomly selected. In comparing the demographic characteristics of the two groups, a statistically significant difference in median income by census tract between the two groups was found. Income is not recorded on these records but does parallel the median income of census tract of residence. Therefore, to study utilization patterns with minimal impact by issues of economic access, all births from census tracts in which the median family income was below $10,000 or not specified were excluded from analysis.

The study considered 524 physician families (90 of which had a physician as mother) and 657 nonphysician families. There was a significant difference in maternal age between the two groups. All analyses, therefore, were stratified by maternal age using five-year intervals, and a Mantel-Haenszel (odds ratio) summary statistic was calculated as an estimate of the relative risk.[8] The two groups were then compared with respect to numerous other maternal risk factors and significant fetal outcomes.

Rates for first and second trimester (midtrimester) amniocentesis were analyzed together since most indications for amniocentesis are the same in this time span. Advanced maternal age (35 years old or older), previous birth with chromosomal abnormality or neural tube defect or a family history of a dominant Mendelian disorder are some of the accepted indications for midtrimester amniocentesis. Third trimester amniocentesis, which is usually indicated for complications of pregnancy, was analyzed separately.

From the Division of Rheumatology, Department of Medicine, Pacific Medical Center and University of Washington, Seattle (Dr Dugowson), and The Health Data Institute, Lexington, Massachusetts (Dr Holland).

Reprint requests to Carin E. Dugowson, MD, MPH, Pacific Medical Center, 1200 12th Ave South, Seattle, WA 98144.

## Results

*Population Characteristics*

Table 1 illustrates the demographic characteristics of the physician and nonphysician families. Maternal age for physician births was found to be higher than that for the nonphysician population. The mean maternal age for nonphysician families was 26.8 years and for physician families 31.3 years ($P = .001$). The mean age for female physicians was 33.1 years.

In contrast, the two groups were quite similar when compared for maternal health problems such as hypertension and diabetes mellitus, number of previous pregnancies and number of prenatal visits. Likewise, the overall incidence of complications of pregnancy was similar (7.2% for nonphysicians versus 5.9% for physicians).

TABLE 1.—*Characteristics of Physician and Nonphysician Families*

| *Maternal and Pregnancy Characteristics* | *Nonphysician Families* | | *Physician Families* | | P *Value* |
|---|---|---|---|---|---|
| Mean maternal age, years | 26.8* | (5.04)† | 31.3 | (3.4) | .001 |
| Number of prior pregnancies | 1.4 | (3.66) | 1.2 | (1.2) | >.05 |
| Number of prenatal visits | 11.9 | (6.64) | 12.1 | (8.15) | >.05 |
| Systemic illness, % | 2.1 | | 2.2 | | >.05 |
| Complications of pregnancy, % | 7.2 | | 5.9 | | >.05 |

*Mean.
†Standard deviation.

TABLE 2.—*Characteristics of Labor and Neonate*

| *Characteristics* | *Nonphysician Families* | | *Physician Families* | | P *Value* |
|---|---|---|---|---|---|
| *Labor* | | | | | |
| Spontaneous delivery, % | 59.6 | | 57.8 | | >.05 |
| Induced labor, % | 1.9 | | 1.7 | | >.05 |
| Prolonged labor, % | 2.1 | | 2.9 | | >.05 |
| Complications of labor, % | 12.5 | | 16.2 | | >.05 |
| *Neonate* | | | | | |
| Apgar 5 minutes | 8.9 | (0.83) | 8.9 | (.76) | >.05 |
| Mean birth weight, grams | 3,440.0 | (577) | 3,483.0 | (550) | >.05 |
| Absence of birth trauma, % | 4.6 | | 4.2 | | >.05 |

*Mean.
†Standard deviation.

TABLE 3.—*Use of Obstetric Technology in Physician-Nonphysician Families—Age-Adjusted Stratified Analysis*

| *Obstetric Technology* | *Relative Risk* | P*Value* |
|---|---|---|
| *Amniocentesis* | | |
| All physician families | 1.65 | >.046 |
| All female physicians | 3.09 | >.0001 |
| Female physicians aged 30-34 years | 5.54 | >.0023 |
| *Primary Cesarean Section* | | |
| All physician families | 1.56 | >.043 |
| All female physicians | 2.14 | >.003 |
| Female physicians aged 25-29 years | 4.83 | >.009 |
| *Low Forceps* | | |
| All physician families | 0.60 | >.0005 |

Neonatal outcomes and characteristics of labor (Table 2) also showed the two groups to be quite similar. Mean birth weights for the two groups differed by only 43 grams. Apgar scores at one minute and five minutes and the incidence of birth trauma were almost identical in the two groups. Comparison of the incidence of induced labor, prolonged labor and spontaneous delivery showed no statistical difference between the two groups. Therefore, we concluded that physician families were comparable to nonphysician families in maternal characteristics before and during pregnancy and characteristics and measures of neonatal outcomes.

*The Use of Obstetric Technology*

*Midtrimester amniocentesis.* Physician families used midtrimester amniocentesis more often and at an earlier age than did their nonphysician counterparts. The overall incidence of midtrimester amniocentesis in the physician families was 10.1% compared with 2.5% in nonphysician families ($P = .0001$). Stratified analysis (Table 3) showed an overall age-adjusted relative risk (RR) for midtrimester amniocentesis of 1.65 ($P = .046$) for physician families, with amniocentesis rates statistically higher for all age strata when compared with nonphysician families. Separate analysis of female physicians showed an age-adjusted relative risk of 3.09 ($P = .0001$). In the 30- to 34-year-old group, women physicians had midtrimester amniocentesis at 5.54 times the rate of their nonphysician counterparts ($P = .002$). By contrast, there was little observed difference in third trimester amniocentesis rates among the three groups.

*Primary cesarean section.* Similar findings were obtained in the analysis of primary cesarean section. Despite the lack of evidence of antecedent problems or mean birth-weight differences between the two groups, physician families again used this procedure more and at a younger maternal age than the nonphysician group, with an age-adjusted relative risk of 1.56 ($P = .043$). On an age-adjusted basis, women physicians used cesarean section more than twice as often as the comparison group (RR 2.14 [$P = .003$]). There was little difference found in the use of repeat cesarean section between physician and nonphysician families; however, sample size was quite small.

*Other obstetric technologies.* Differences in the use of low forceps and alternate birthing centers also appeared in the analysis. Physicians were almost half as likely to have low forceps used during delivery as their nonphysician counterparts (RR .60 [$P = .05$]). Finally, in the three years of our study only 1.1% of physician births occurred in nonhospital locations such as home or birthing centers while 5.7% of nonphysician families used these alternatives.

## Discussion and Conclusions

Pronounced differences in utilization of obstetrical technology between physician and nonphysician families were shown in this study. Multiple comparisons of both prenatal risk factors and birth outcome did not identify differences between physician and nonphysician families that would explain these differences in behavior.

Other studies have also found differences in the manner in which physicians and their families use medical services. A study of radiologists and their families showed their use of diagnostic x-ray procedures to be much more frequent than that of a comparison group of nonradiologist physicians.[4] In contrast, a survey of physicians' personal use of preventive

screening practices found their behavior to be erratic with both underuse and overuse of some services.[5]

In Bunker and Brown's study,[3] surgical rates for a variety of common operations were ascertained for physicians, attorneys, businessmen and ministers and their spouses. Although the authors' hypothesis was that physicians would have fewer surgical procedures than lay people, this was not confirmed by the data. Most procedures were carried out with equal frequency in all groups; however, physicians and their spouses more often had undergone thyroidectomy and appendectomy.

Furthermore, women physicians and attorneys had significantly lower rates of hysterectomy than the spouses of male physicians or attorneys. This suggests that surgical rates among physicians do not simply reflect a general disposition to utilize these services or not but that specific choices are being made. Our study supports such a thesis.

We feel these observations reflect the characteristics of physicians and their unique medical knowledge. In contrast to most expectant parents, many physicians have seen suboptimal obstetric outcomes during their training. Presumably, they have confidence in medical technology and it is plausible that they choose to use this technology at such a personally critical juncture. Other explanations, however, are possible. Unknown, and of great importance, is whether physicians are generally treated by specialists who use these technologies at higher rates. Such selection might explain these findings equally well.

Since physicians guide their patients' behavior, health planners should note the manner in which physicians use health care services. As the population becomes more sophisticated medically, one can speculate that the behavior of the general population will increasingly mirror that of physicians.

This preliminary study is limited in several respects. The study groups are small and represent only one urban county in Washington State. Confounding by socioeconomic status may still be present since specific information on income and other socioeconomic data is not indicated on the record. Physicians in different specialties may make notably different medical care choices. Utilization trends may also be changing over time. Finally, the beliefs of neither the providers nor the recipients of care, which are central to understanding behavior, can be obtained from birth records. Nonetheless, the choices made for obstetric care, especially by women physicians, are striking. If similar changes occur in the general population, the consequences of these utilization trends may be substantial in both personnel and equipment demands. Health care planners will be obliged to address these issues in the future.

#### REFERENCES

1. Somers AR, Somers HM: Proposed framework for health and health care policies. Inquiry 1977; 14:115-170

2. Thomas L: Your very good health. N Engl J Med 1972; 287:761-762

3. Bunker JP, Brown BW Jr: The physician-patient as an informed consumer of surgical services. N Engl J Med 1974; 290:1051-1055

4. Jessup GL Jr, Silverman C: Personal usage of medical radiological procedures by radiologists, pathologists and their families. Am J Epidemiol 1981; 114:53-62

5. Shlian DM: Health care utilization among physicians in a large prepaid medical group. J Fam Pract 1982; 14:1091-1094

6. Fisher NL: Utilization of Midtrimester Amniocenteses in the State of Washington, 1979: A Descriptive Study of Prenatal Diagnosis Patterns, unpublished MPH thesis. Seattle, University of Washington, 1982

7. Hook EB, Schreinemachers DM: Trends in utilization of prenatal cytogenetic diagnosis by New York State Residents in 1979 and 1980. Am J Public Health 1983; 73:198-202

8. Schlesselman JJ: Case Control Studies: Design, Conduct, Analysis. New York and Oxford, Oxford Univ Press, 1982, pp 181-185

Public Health and Preventive Medicine

# Injuries and Fatalities Associated With Off-Road Three-Wheeled All-Terrain Vehicles

C. MACK SEWELL, PhD; JEFFREY S. PINE, MSPH, *and* HARRY F. HULL, MD, *Santa Fe, New Mexico*

*This is one of a series of articles from western state public health departments.*

In the past several years, three-wheeled all-terrain vehicles (ATVs) have gained widespread popularity in the United States. Originally used by farmers and sportsmen for transportation away from established roads, ATVs are now predominantly used for purely recreational purposes. These three-wheeled motorcycles with large balloonlike tires have engine displacements that vary from 60 to 400 cc and can attain speeds of up to 70 mph. They range in cost from about $600 to more than $2,500, and weigh from 75 to more than 180 kg (170 to 400 lb). Driving skills for ATVs are considerably different from those required for driving a car or a two-wheeled motorcycle. The Consumer Product Safety Commission (CPSC) has noted a sharp increase in serious injuries and fatalities associated with the use of ATVs. The estimated number of ATV-related injuries reported through CPSC's National Electronic Injury Surveillance System increased from 8,600 in 1982 to 85,000 in 1985. As of July 1986, more than 559 ATV-related deaths had been reported to the CPSC. It is estimated that over 750,000 ATVs were sold in the United States in 1985, and sales of these vehicles are continuing to increase dramatically. Data collected by the CPSC showed that 19% of the injuries involving ATVs have occurred to users younger than 12 years, with 46% occurring among users younger than 16 years.[1] The increasing use of these vehicles coupled with the young age of accident victims has prompted several state health departments to monitor injuries and fatalities associated with ATVs. In New Mexico, the Health and Environment Department is conducting a prospective study of ATV-related injuries and deaths in conjunction with several hospitals and the state's Office of the Medical Investigator. The following incident illustrates several problems with the use of ATVs.

## Report of a Case

On August 27, 1985, a 14-year-old unhelmeted girl was riding an ATV along an irrigation ditch bank road when she apparently locked up the front brake and was thrown over the vehicle. She struck the corner of the metal frame of an irrigation channel lock with her head, fell into the irrigation ditch and drowned. Her body was found about two miles downstream by her brother. The medical investigator report indicated the cause of death as drowning due to a skull fracture.

## Discussion

This incident shows several problems associated with the use of ATVs. First, the operator of this ATV was young and unlicensed. Second, she was not wearing a helmet or other protective gear. Third, she was not being supervised by an adult. Finally, the driver did not have the experience and agility to properly operate the ATV. Although ATVs were designed for use off road, by a single rider, the CPSC survey[1] found that 35% of ATV accidents involved practices that the ATV manufacturers warned against: carrying passengers and driving on paved roads.

A recent study in Alaska[2] identified 20 deaths and 538 injuries in a 24-month period that were associated with three-wheeled ATVs. Six accident victims received severe head or spinal cord injuries and are now permanently disabled and require long-term skilled care. Interestingly, 63% of incidents in Alaska occurred on established roads (probably due to the use of ATVs for subsistence and recreational hunting, fishing and basic transportation). Significant risk factors associated with ATV injuries included alcohol use, lack of helmet use, rider inexperience and inattention and excessive speed. Their data suggested that 60% of the fatalities may have been prevented if a helmet had been worn.

Cogbill and colleagues suggest that morbidity and mortality due to ATV-associated accidents may be reduced through three approaches: (1) increased awareness of the potential dangers of these vehicles, (2) protective devices and (3) regulation of three-wheeled motorcycles and their drivers.[3] It is clear that these vehicles should only be operated by experienced drivers who have the required skills, strength and agility. They should be used off the road (the use for which they were designed) with only one rider per vehicle. Protective gear such as boots, long pants, gloves, goggles and a proper helmet are essential for any ATV rider. Young, inexperienced or unprotected persons should not be riding or operating an ATV.

We recommend that legislative efforts be directed toward young ATV riders. Specifically, ATV operators should be required to have the equivalent of a motorcycle operator's license and be at least 15 years of age. Helmet use should be mandatory for these and other types of motorcycles. ATVs designed exclusively for very young riders should be banned.

(Sewell CM, Pine JS, Hull HF: Injuries and fatalities associated with off-road three-wheeled all-terrain vehicles. West J Med 1987 Apr; 146:497-498)

From the Office of Epidemiology and the Injury Control Program, New Mexico Health and Environment Department, Santa Fe, New Mexico.
Reprint requests to C. Mack Sewell, PhD, Office of Epidemiology, PO Box 968, Santa Fe, NM 87504-0968.

ABBREVIATIONS USED IN TEXT

ATV = all-terrain vehicle
CPSC = Consumer Product Safety Commission

Furthermore, it is essential that police enforce existing laws that prohibit the use of unregistered vehicles (most ATVs) on public roads. Manufacturers and retailers can assist injury prevention efforts by emphasizing the use of protective gear, such as helmets, and by marketing ATVs only for older ATV riders. States can develop safety training manuals[4] and sponsor ATV safe-riding courses. The need for training is shown by the fact that 47% of those injured by collision and 26% of those injured when the vehicle overturned had less than a month's driving experience.[1] Studies that compare the relative stability of three-wheeled ATVs with two- and four-wheeled cycles are needed. Preliminary data suggest that the three-wheeled ATVs are more dangerous than four-wheeled ATVs.[5] Hospital-based studies to document the extent of the problem could be better achieved by improving medical record documentation and coding of ATV accidents.

REFERENCES

1. Survey of All-Terrain Vehicle Related Injuries (1985)—Preliminary Report. Consumer Product Safety Commission, 1985

2. Smith SM, Middaugh JP: Injuries associated with three-wheeled, all-terrain vehicles, Alaska, 1983 and 1984. JAMA 1985; 255:2454-2458

3. Cogbill TH, Landercasper J, Metheny JA: Three-wheeler accidents (Letter). JAMA 1985; 254:1037

4. Minnesota Department of Natural Resources, Law Enforcement Division: Minnesota ATV Safety Training Manual. St Paul, Outdoor Empire Publishing, 1985

5. Trager GW, Graymar G: Accidents and all-terrain vehicles (Letter). JAMA 1986; 255:2160-2161

## Medical Practice Question

EDITOR'S NOTE: *From time to time medical practice questions from organizations with a legitimate interest in the information are referred to the Scientific Board by the Quality Care Review Commission of the California Medical Association. The opinions offered are based on training, experience and literature reviewed by specialists. These opinions are, however, informational only and should not be interpreted as directives, instructions or policy statements.*

### Diagnosis of Obstructive Sleep Apnea in Children

**QUESTION:**

*What criteria are necessary for the diagnosis of obstructive sleep apnea in children?*

**OPINION:**

In the opinion of the Scientific Advisory Panels on Otolaryngology/Head and Neck Surgery and Pediatrics, the diagnosis of obstructive sleep apnea, described physiologically as a cessation of airflow at the nose and mouth with the concomitant occurrence of inspiratory efforts, can be established in children by a thorough history and physical examination. Criteria necessary to make this diagnosis must include a history of snoring and apnea during sleep (documented by reliable observers) and usually include some or many of the following signs: restless sleep and abnormal sleep positions; repetitive awakening at night; nocturnal enuresis; daytime somnolence; mouth breathing while awake; large tonsils and adenoids; craniofacial abnormalities; irritability, and hyperactivity.

Though it is not always necessary, the polysomnogram is the only sleep study that can provide a definitive diagnosis of obstructive sleep apnea. This multi-channel recording of physiologic parameters during sleep varies in its components from center to center. To diagnose significant sleep apnea, however, it must include a measure of airflow, chest wall movement and oxygenation. Significant obstructive apnea on a polysomnogram is defined as the absence of airflow in the presence of chest wall movement for more than 15 seconds (or of shorter duration if associated with arrhythmia, hypoxemia and hypercarbia). Significant partial obstructive apnea is defined as an impairment or partial absence of airflow associated with the three conditions just noted. Polysomnography should be used when the results will clearly make a difference in the differential diagnosis or in the treatment plan. The pneumogram, which measures impedance respiration and heart rate, is not polysomnography and is totally inappropriate for the study of suspected obstructive sleep apnea.

Finally, obstructive sleep apnea in children must *not* be confused with apnea of infancy, the so-called near-miss sudden infant death syndrome, which is generally defined as an unexplained episode of cessation of breathing for 20 seconds or longer, or a shorter respiratory pause associated with bradycardia, cyanosis or pallor.

# Using Resistant Behaviors in the Treatment of Alcoholic Patients

LA VERA M. CRAWLEY, MD, *San Francisco*

Patients with chronic alcoholism are commonly described as showing resistant behaviors that can prevent their active or successful participation in most prescribed treatment programs.[1-7] The phenomenon of resistance is not unique to alcoholic patients and has been well recognized, described and theoretically explained in both family therapy and medical literature.[8-12] Patient resistance has been reported in such cases as noncompletion of homework assignments, noncompliance to medication regimens or unwillingness to discuss major problems. In the case of "dropouts," clinical research results and subsequent data analyses have been greatly affected by this aspect of resistance.[8,13]

Some persons may resist therapeutic suggestions when they perceive that their decision-making powers are being threatened.[8,14] In an attempt to reassert their power, they may respond by denying the presence or magnitude of a problem, by escalating their behavior or by simply refusing to continue with treatment. As a means of maintaining a sense of personal identity or to uphold the family rules, families may likewise react defiantly to external attempts to influence them.[10]

Resistance can be defined as all behaviors that prevent a person or a family from reaching a therapeutic goal. This definition suggests, then, that the conduct of health providers can also contribute to patient resistance.[10] Negative physician attitudes and confrontive behaviors can create barriers toward patients that increase the likelihood of noncompliance.[15]

In the case of alcoholic patients, those who are labeled resistant often appear unmotivated, oppositional or noncompliant to therapy. Their denial is a major defense that allows the problem to continue.[4] While experiencing a physical and psychological addiction to alcohol over which they feel powerless, resistance provides a means to maintain a sense of control in their lives. The continual insistence by a physician for an alcoholic patient to change may compound the dilemma by creating a doctor-patient power struggle in which potentially everyone could lose. If, however, a situation could be developed whereby the focus of a patient's resistance could be strategically mirrored or redirected, then the same behaviors used to maintain drinking could be used effectively to mobilize toward positive change.[1,4,5] This paradoxical approach has been successful in eliminating resistance by promoting greater cooperation between physician and patient and by motivating a patient with alcoholism to take control of his or her actions.

## Paradoxical Interventions

The therapeutic intervention described as a paradoxical instruction, which has been extensively reviewed and used by a variety of health care professionals, is one alternative technique that may be useful in working with resistant alcoholic patients.[16-19] By definition, a paradoxical directive is a well-defined, seemingly contradictory instruction that creates a therapeutic double bind by encouraging a patient to "change by not changing."[20-23] For example, by avoiding the overt direction to stop drinking and, perhaps, even encouraging some aspect of that behavior, the patient must shift the focus of resistance to a new direction. By also connecting the drinking behavior to the function it serves in the system, a covert message is relayed that forces the patient to experience a reorganization of thought about his or her alcoholic behavior. This mental process is essential in some alcoholic patients for change to occur.[4,20]

Paradoxical interventions should not, in and of themselves, be construed as a complete treatment modality. Rather, this is simply a stance to take with select patients that may assist them in shifting symptoms from destructive modes to less destructive ones. As such, various paradoxical strategies and techniques are available for use with alcoholic patients.[1,4] In one method, some aspect of the drinking behavior, such as the time or place of occurrence, is viewed as a symptom. The physician first reframes the symptom as having a positive connotation and then "prescribes" the symptom to the patient. Both the reframing component and the symptom prescription are stated in a tentative yet plausible, intelligible manner that sounds neither punitive nor facetious.[4,19]

## Reframing

Reframing is a verbal explanation that changes the contextual meaning of a particular situation or behavior.[1,23] It allows the physician, patient and family to interpret the symptom as serving some useful function that in turn makes possible new consequences.[1] The reframe is derived from information previously gathered regarding the patient's life-style or family structure. For example, the drinking behavior of an alcoholic man who experienced difficulties in his marital or family relationships can be redefined as a means to control intimacy versus distance in those relationships—for example, "Your drinking seems to provide an opportunity for you to remove yourself from an unpleasant home life and thus avoid painful confrontations. It is very noble of you to want to protect yourself and your family."

## Symptom Prescription

Once the behavior has been reframed, the patient is asked to diligently practice the problematic behavior as opposed to

(Crawley LM: Using resistant behaviors in the treatment of alcoholic patients. West J Med 1987 Apr; 146:499-501)

From the Family Practice Residency Program, Division of Family and Community Medicine, San Francisco General Hospital Medical Center and the University of California, San Francisco, School of Medicine. Dr Crawley is now Alcohol Services Coordinator at Inscription House Indian Health Center, Shonto, Arizona.

Reprint requests to LaVera M. Crawley, MD, Inscription House Indian Health Center, PO Box 7397, Shonto, AZ 86054.

having it appear out of the realm of unconscious or addictive control. The "prescription" can either be a redirection, such as suggesting a change in the time or place that the behavior normally occurs, or a direction to either escalate or increase the frequency of the identified aspect of drinking behavior.[4,17,23] For example, once the pattern of drinking has been defined as serving a protective function, a patient is encouraged to better protect her or himself by remaining close to home while drinking—that is, "You could probably protect yourself and your family much better if you could keep a closer eye on things. The next time that you decide to drink, I suggest that you find a private place within your own home, isolated enough so that you can still avoid painful confrontations, but close enough for you to keep a watch over things." The paradoxical instruction may also be effective if framed in the form of a sharing question. As an alternative, the patient can be asked, "Though there are aspects of your drinking that may be genuinely noble in protecting your family, in what other ways can you protect them?"

Symptom prescription will usually seem absurd, or at least surprising to most patients, yet it is that absurdity that accounts for its potential success. It allows an alcoholic person to momentarily place him or herself at a distance from the drinking behavior. This detachment can assist the patient in placing the symptom under voluntary control.[17]

Before using symptom prescription, however, the physician should be especially alerted to the possibility of a detrimental escalation of the drinking behavior resulting from the patient's misinterpretation of this stance. This technique does not encourage the physician to become overly indulgent of deleterious behaviors, nor does it imply that they become "alcohol pushers." The goal of this intervention is to enlarge the alcoholic's view of "uncontrolled" behaviors. Therefore, it is recommended that the physician not use the actual intake of alcohol as an isolated symptom prescription but rather shift the focus away from the use of alcohol and onto those behaviors that surround its use. This is facilitated by initially using an affirmative reframe.[24]

The paradoxical approach should be reserved for ongoing, repetitive patterns of behavior that show failed responses to traditional interventions. Its use is contraindicated when resistance, oppositional behavior or power struggles are absent, in extremely disorganized or chaotic persons or families or when escalation of a behavior may have dangerous consequences.[4,23] Indeed, its use should be discontinued if crisis situations develop in which the patient or family may need more external structure or control. These techniques should be completely individualized and used only in the context of a caring therapeutic relationship in which trust, a thorough knowledge of the patient's medical and psychosocial history and continuity are developed and where such risks as escalation or misinterpretation can be minimized.

## Case Examples

### *Patient 1*

A 32-year-old alcoholic man was followed for intermittent constipation and hemorrhoids that appeared to be related to periods of "binge" drinking. The patient's observed drinking pattern was that of binging, decreased food intake, constipation and hemorrhoids. He related this behavior to his frustrations as an unskilled laborer in the job market. He said he did not have a drinking problem as he was able to remain sober for months at a time. He was consistently reluctant to discuss the issue further. The physician repeatedly encouraged him to seek alcoholic counseling, yet, at each succeeding visit, the patient would say he had not followed up on any treatment recommendations.

Given this history, a paradoxical strategy was devised that combined both his concern for his gastrointestinal condition and the financial employment stressors that seemed to precipitate his binging. It also acknowledged his ability to maintain a limited period of sobriety. The physician reframed the patient's behavior in a positive manner by saying, "Your drinking seems to make a lot of sense to me. It eases some of your frustrations about working and it certainly takes your mind off things like eating or finding food. I bet when things get tough for you with finances or with finding a job, it becomes difficult to focus on getting three square meals a day." The prescription then followed, "I'm not going to tell you to stop drinking. You have already shown that you can do that if you have to. When it becomes necessary for you to go on another binge, however, I want you to do something that can help prevent your constipation and hemorrhoids. I want you to take fiber and these vitamin supplements and do your best to maintain a healthy diet throughout the binge."

The physician maintained this strategy during subsequent visits. By avoiding the instruction to seek counseling and by acknowledging the patient's competence, the physician eliminated the conditions for opposition and resistance. The paradoxical stance allowed the patient to connect a conscious activity—that is, taking food supplements—with an involuntary action—that is, the uncontrollable urge to drink—thus providing him an opportunity to exercise some voluntary control over his drinking behavior. This approach not only enabled him to experience increased periods of sobriety, but eventually helped motivate him to enter an alcoholism treatment program.

### *Patient 2*

The patient, a 54-year-old woman, was seen for depression that she related to her husband's drinking behavior. They lived in a large household that included several children and grandchildren ranging in age from 8 to 34 years. This living arrangement was a source of anxiety for the patient's husband who felt that the five adult children and their offspring should move out on their own. The patient was adamant that they remain in the home with her and did not identify her support of them as burdensome. She cited her husband's drinking as the only problem. Her husband had been quite resistant to seeking help for alcohol abuse. The conflict around the children, however, provided an opportunity to speak with them as a couple. Both the patient and her husband agreed to attend counseling sessions to discuss their parenting dilemma.

The patient voiced her extreme frustration with the lack of help that her alcoholic husband offered in caring for the household. It became apparent, however, that she would unintentionally sabotage any contribution that he made. For example, whenever he verbally reprimanded the children or encouraged their independence, she would actively disagree and defend the children against her husband. She felt that she needed to compensate for his drinking by taking complete responsibility for the children.

The physician felt that by being overly competent, the patient actually contributed to her husband's peripheral position in the family. By viewing his drinking as a means to maintain their family homeostasis, the physician reframed the

husband's behavior as the thoughtful and caring way in which he empowered his wife. By sacrificing his position as a strong, effective husband and father figure, he allowed his family to stay together according to his wife's wishes. A double bind was created by suggesting to the wife that she continue to let her husband drink to maintain her position as head of the household and to allow the children to remain dependent and in the home. She was also encouraged to take on even more responsibilities as a way to show her appreciation for her husband's sacrifice. Any sign of sobriety or assistance from her husband was reframed as a risk to her identity as strong and capable. They were both given information about Al-Anon and Alcoholics Anonymous, along with a warning that recovery or other changes might require a shift in their current roles. The physician further cautioned them to consider the consequences of such a change in their family system.

Although the patient found the reframe to be somewhat ludicrous, she also thought it contained an element of truth. Her paradoxical prescription, along with the support of Al-Anon, increased her insight into how she had contributed to the problem. By giving her husband's behavior a positive connotation, this intervention enabled him to become less resistant toward the physician and more cooperative with treatment recommendations.

The success of this paradoxical strategy was based on shifting the focus away from the alcoholic person and onto the larger system that sustained the drinking behavior. In such cases where the family system plays a critical role in the repetitive use of alcohol, any change in the alcoholic homeostasis resulting from a successful therapeutic intervention can create an initial period of instability.[4] Such difficulties as anxiety, relapse or family crises are predictable as alcoholic persons and their families adjust to new life-style changes that accompany a move toward control of the drinking behavior.

## REFERENCES


1. Weinstein DL: Strategic treatment techniques in alcoholism treatment: Valuable tools for dealing with resistance. Alcohol Treat Q 1985; 2:25-35
2. Berger F: Alcoholism rehabilitation: A supportive approach. Hosp Community Psychiatry 1983; 34:1040-1043
3. Twerski AJ: Early intervention in alcoholism: Confrontational techniques. Hosp Community Psychiatry 1983; 34:1027-1030
4. Shore JJ: Use of paradox in the treatment of alcoholism. Health Soc Work 1981; 6:11-20
5. Greene GJ, Sattin DB: A paradoxical treatment format for anxiety related somatic complaints: Four case studies. Fam Syst Med 1985; 3:197-204
6. Rees DW: Health beliefs and compliance with alcoholism treatment. J Stud Alcohol 1985; 46:517-527
7. Clark WD: Alcoholism: Blocks to diagnosis and treatment. Am J Med 1981; 71:275-286
8. Jahn DJ, Lichstein KL: The resistive client—A neglected phenomenon in behavior therapy. Behav Modif 1980; 4:303-320
9. Chamberlain P, Patterson G, Reid J, et al: Observation of client resistance. Behav Ther 1984; 15:144-155
10. Anderson C, Stewart S: Resistance, chap 1, Mastering Resistance. New York, Guilford Press, 1983, pp 1-38
11. Stein HF, Pontious JM: Family and beyond: The larger context of noncompliance. Fam Syst Med 1985; 3:179-189
12. Amundson LH: A review of patient compliance: Magnitude and determinants. Cont Educ Fam Pract 1985; 20:621-630
13. Castle WM: Statistics in Operation. New York, Churchill Livingstone Press, 1979, p 39
14. Brehm JW: A theory of psychological reactance, chap 1, A Theory of Psychological Reactance. New York, Academic Press, 1966, pp 1-16
15. Patterson G, Forgatch M: Therapist behavior as a determinant for client noncompliance: A paradox for the behavior modifier. J Consult Clin Psychol 1985; 53:846-851
16. Weeks G, Abate L: A bibliography of paradoxical methods in psychotherapy of family systems. Fam Process 1978; 17:95-98
17. Raskin DE, Klein ZE: Losing a symptom through keeping it. Arch Gen Psych 1976; 33:548-555
18. Ascher ML: Paradoxical intention in the treatment of urinary retention. Behav Res Ther 1979; 17:267-270
19. Papp P: The Greek chorus and other techniques of paradoxical therapy. Fam Process 1980; 19:45-57
20. De Shazer S: The death of resistance. Fam Process 1984; 23:11-21
21. Ascher ML, Turner RM: A comparison of two methods for the administration of paradoxical intention. Behav Res Ther 1980; 18:121-126
22. Dell P: Some irreverent thoughts on paradox. Fam Process 1981; 20:37-51
23. Fisher L, Anderson A, Jones JE: Types of paradoxical intervention and indications/contraindications for use in clinical practice. Fam Process 1981; 20:25-35
24. Kolko DJ, Milan MA: Reframing and paradoxical instruction to overcome 'resistance' in the treatment of delinquent youths: A multiple baseline analysis. J Consult Clin Psychol 1983; 51:655-660

# Teaching Spanish and Cross-cultural Sensitivity to Medical Students

TERESA GONZALEZ-LEE, PhD, *and* HAROLD J. SIMON, MD, PhD, *La Jolla, California*

The notion that cultural factors affect the quality of the health care provided to and received by people belonging to any particular ethnic group has been recognized and addressed in the literature.[1,2] Similarly, reports of difficulties encountered by physicians treating patients from other cultures have pointed to a compelling need to improve the tools of communications.[3] The Department of Community and Family Medicine at the University of California, San Diego (UCSD), and at the UCSD Medical Center has also encountered such problems. Aware that the communication process is a vital factor in patient care, the department has undertaken the task of teaching Spanish—the predominant foreign language in the region—to both undergraduate and graduate medical students. Operating on the premise that effective communication encompasses both linguistic and cultural perceptions of verbal and nonverbal behaviors, the department faculty has sought the advice and expertise of the UCSD Department of Linguistics and of the Latino medical community in a search for ways and means to bridge the cultural differences between the predominantly Anglo-American medical students and Latino patients. As a result, health care providers and the teaching faculty have designed two specialized Spanish and cross-cultural programs, one for the second-year class of medical students on the campus of the School of Medicine in La Jolla, California, and the other for family medicine residents at UCSD Medical Center in San Diego.

The demographics and location of San Diego provided an additional rationale for establishing these programs. The proximity of San Diego to the US-Mexican border ensures a continuous traffic of Mexicans and other Latino Americans looking for better living conditions and medical services in the United States. This "floating" population, added to the large number of Mexican-Americans who live in San Diego, increases the percentage of Latinos to 25% of the total population potentially seeking medical care in this bilingual, bicultural border area. Thus, medical students and residents in the teaching hospitals in San Diego see a large number of Spanish-speaking patients in need of medical attention.

A third factor motivating the development of these programs at UCSD School of Medicine was the perception that complex changes now characterize the continuing evolution of the medical profession. As Starr suggests in *The Social Transformation of American Medicine*, the growing surplus of physicians in the United States is leading to competition for patients, among other new phenomena.[4] To be better equipped to face the future, health care providers may need or wish to acquire improved cross-cultural skills by acquiring Spanish to enhance communication with Latino patients.

In this article, we describe a novel approach to this increasingly important problem; namely, the need to overcome language and other cultural barriers to enable health care professionals to understand the concepts of health and illness prevalent in other cultures and to teach the tenets of science-based medicine to patients from diverse cultural backgrounds.

## Description of the Programs

*Objectives*

The objectives of the two programs are identical: to develop a high level of cross-cultural understanding and sensitivity among students by means of a language acquisition process and through carefully supervised contacts with Latino patients. Kristal and co-workers have specified the cross-cultural learning objectives for a family medicine residency training program, in that "culture forms an important part of the identity of every patient and . . . culture-related stresses are known to induce illness."[5] The implication is that health care providers should strive to achieve a working level of cross-cultural sophistication. The following addresses the concepts underlying the programs and the skills and knowledge to be acquired by the students.

*Concepts*

- Culture dictates the norm of behavior for a particular group.
- Diversity, however, exists in a group in the way each person reacts to a specific situation. Thus, Mexican-Americans react differently to a particular situation than do more recent Mexican immigrants because of greater acculturation and as a result of socioeconomic and educational differences.
- Health beliefs affect patients' understanding of illness and compliance with medical instructions.
- Complex cultural perceptions, however, affect views of and responses to health and illness, life and death and other dichotomies such as viral infection versus hex or *mal puesto*, the concept of reincarnation versus heaven or hell and so forth.

*Skills*

- Ability to understand, speak, read and write Spanish with a full command of grammar and medical terms.
- Ability to use the medical context to decode meaning from patients' language as they describe symptoms and their concepts of cause.
- Ability to interpret verbal and nonverbal messages from patients of another culture.

(Gonzalez-Lee T, Simon HJ: Teaching Spanish and cross-cultural sensitivity to medical students [In the Forefront]. West J Med 1987 Apr; 146:502-504)

From the Department of Community and Family Medicine, University of California, San Diego, School of Medicine, La Jolla.

This study was supported in part by Cooperative Agreement No. 2 U76 PE 00053-07 with the Division of Medicine, Bureau of Health Professions, Health Resources and Services Administration, US Department of Health and Human Services. The AHEC program is a cooperative endeavor of the San Diego/Imperial Rural Area Health Education Center, Palomar Community College, and the University of California, San Diego, School of Medicine.

Reprint requests to Harold J. Simon, MD, PhD, Professor of International Health Policy, Dept of Community and Family Medicine, M-022, La Jolla, CA 92093.

• Oral proficiency in medical Spanish, including the ability to communicate in Spanish when interviewing a patient and doing physical examinations.

*Knowledge*

Within the Mexican and Mexican-American culture, to understand

• Family structure with its diverse variants (nuclear, extended, single parent);
• Foods and nutrition;
• Customs and celebrations;
• Attitudes about health and illness and important life processes in general, such as birth, puberty, maturity, death and dying;
• Effects of religion on concepts of health and illness, life and death and other dichotomies, and
• Values and ethics among Latinos.

## Methods

The objectives are identical, but the methods used differ between the two programs.

*The Program of Spanish and Cross-cultural Instruction for Family Medicine Residents*

The various components of the program as originally conceived are described by Kristal and associates and consist of (1) a Spanish language course, (2) a clinical rotation in a community health clinic catering to a medically underserved Latino population, (3) a preceptorship in home-based health education and counseling for Spanish-speaking families and (4) a set of cross-cultural sensitivity training activities integrated into the behavioral science program of the residency. The program at UCSD Medical Center was established in 1979 as an integral part of the required curriculum for family medicine residents. It has been implemented as a tutorial program for all second-year residents and for some faculty and staff, usually two to three a year.

The Spanish language course has two major components. The academic component consists of a course integrated into the curriculum within the rubric of cross-cultural medicine. The second part consists of immersion in the Latino culture in conjunction with the clinical rotation at the San Ysidro Clinic, a border health care center. Actual contact time with language and cross-cultural immersion includes one hour of private tutorial weekly in addition to interactions with Latino patients at both the UCSD Medical Center and the San Ysidro Clinic. This amounts to more than ten hours a week of cultural immersion and clinical experiences in Spanish.

The Spanish program is currently undergoing revision. Contemplated changes include replacing the individual tutorials with small group sessions to accommodate the greater number of students wanting to participate in the program. Within the past three years, the objectives of the behavioral science program were integrated into the Spanish course. This includes extension of training in psychosocial interviewing in both English and Spanish for residents whose command of Spanish is sufficiently advanced.

*The Program for Second-Year Students at the School of Medicine*

This program is supported by grants from the San Diego-Imperial Rural Area Health Education Center (SIR/AHEC), the UCSD School of Medicine and from various private donors. It is aimed primarily at second-year medical students who are concurrently learning the principles and practices of history taking and physical examination. Established in 1984, the program enrolled 22% of the second-year class in its first year and 22.5% in the second, the maximum that could be accommodated. Although composed of a series of three "elective" courses given in three consecutive quarters, students are informed that credit will be awarded only for taking the entire three-quarter sequence. Attrition amounted to 4 of 26 students in 1984-1985, and none of the 27 enrolled in 1985-1986, in most cases due to academic difficulties encountered in other courses. Students are prescreened for placement, with prospective beginners being defined as those who have taken less than three years of high school Spanish, or less than one year at the college level, or equivalent. Those with more extensive experience with Spanish are enrolled in the intermediate level class.

The academic component consists of three hours of classroom seminars a week. The cross-cultural clinical experiences are an important aspect of the program. Each week, groups of two to three students visit the offices of Latino physician preceptors in the community who facilitate the language-acquisition process. Students interview four to five Spanish-speaking patients scheduled to be seen by their physician preceptor. Prepared in the classroom setting with pertinent interview questions, students practice their language skills when confronted with a patient in these clinical sessions. Preceptors act as role models and begin by themselves interviewing the patients while the students observe. Gradually, the students' emerging confidence and competence allow them to do the interviewing. By the middle of the school year, the students are left to interview the patients largely on their own, and they report to the preceptor on all the data obtained from the interview.

Clinical sessions represent opportunities to practice Spanish within a medical and cross-cultural context. Students are thus exposed to patients' historical, political and social references that they have to decode.

Preceptors act as role models in various ways. They provide examples of the language as it is normally spoken between patient and physician; they provide cross-cultural expertise because they are themselves bilingual and bicultural, and they demonstrate their medical competence to the students. These physicians were selected because they practice in specialties that lend themselves particularly well to the purposes of the program, such as family medicine, internal medicine and pediatrics. The receptive attitude of the Latino patients also contributes in large part to the students' learning of Spanish. Patients generally welcome students and express appreciation of their efforts to communicate in Spanish.

Clinical sessions demand large blocks of time (three to four hours a week). The total commitment of 12 to 15 hours a week to this program on the part of students who also have to continue their 25 to 30 hours a week in the core curriculum imposes a heavy study load on them. Students, however, continually manifest their interest in and commitment to the Spanish program by regularly attending classes and clinical sessions, through the low attrition rates and in their written evaluations of the course and the preceptors.

*Oral Proficiency in Medical Spanish*

Among the several objectives of the Spanish programs, the most important is that students acquire oral proficiency in medical Spanish. They are expected to acquire the ability to understand and communicate with patients using their natural

flow of language during any medical transaction. Considering the time limitations imposed on both residents and medical students and the advantages of cultural immersion, the natural approach developed by Krashen and Terrel was adopted as the method of choice for these programs.[6] The two components of these programs—an academic component (the seminars) combined with cultural immersion (the clinical sessions)— facilitate compatibility with the natural approach and its double process of "acquisition" and "learning." The point of departure is Terrel's hypothesis that a second language is "acquired" through linguistic inputs provided for our comprehension, and that the most important aspect is "acquisition" of language, not "learning" of rules. Then, the determinant factors in a language and cultural acquisition program for professionals would very likely be assimilation of any linguistic input presented in a meaningful context. In Terrel's words:

> According to the input hypothesis, language acquisition can only take place when a message which is being transmitted is understood; i.e., when the focus is on *what* is being said rather than the *form* of the message. This could be referred to as the Great Paradox of Language Teaching: Language is best taught when it is being used to transmit messages, not when it is explicitly taught for conscious learning.[6]

When the medical context is being optimally used, the singular paradox of teaching a language without actually teaching it—or, better, learning it without being specifically taught it, and yet "acquiring" it—is resolved because messages conveyed with the linguistic input become the foci to be decoded and understood. The task of decoding the linguistic input that provides medically useful information stimulates intellectual activity and heightens motivation, thereby personalizing the experience of grasping the medical issues at hand.

Only rarely do discussions in English focus on how the language works. Therefore, "acquisition" of the language and not its "learning" become critical in programs for professionals. Principal activities involve the use of audiovisual materials, real objects, film strips designed to facilitate natural acquisition of the language and providing the linguistic input that will trigger more understanding and maximize "acquisition."

Several textbooks in medical Spanish have been selected for these programs.[7-12] Nevertheless, the core of these courses consists of teaching and reviewing techniques by means of dialogues designed to facilitate the process of obtaining a medical history. These techniques vary according to the nature of the relationship established between patient and health care provider. They may consist of open-ended interviews in which a patient takes the initiative and engages in open dialogue with the physician; they may consist of more structured interview styles whereby the physician chooses a very active role and guides the interview by posing general or specific questions, or they may consist of interviews using a mutually cooperative approach in which both physician and patient interact in a "dialogue of equals."[13] Regardless of which technique is used, the same goals are sought: namely, to obtain information about the chief complaint; the history of the present illness; the past medical history; the family, social, occupational and cultural histories, and a review of the major organ systems. In selecting an interview style, the physician may have to consider a patient's level of acculturation, educational background, personality and socioeconomic circumstances. The task of interviewing Latino patients becomes more complex when the medical complaints are interspersed with digressions containing historical, folkloric and personal information, all of which become part of the linguistic input to be processed in the mind of the American health care provider to permit him or her to "acquire" medical information as effectively as possible.

### *Effectiveness of the Program*

The Spanish language and cross-cultural sensitivity program at the UCSD Medical Center is in its seventh year. Resident physicians recognize the usefulness of the program at the beginning competency levels because it enables them to establish rapport and work on improving patient-physician interaction. Most graduates of the family medicine residency program remain in California to work in medically underserved areas. Even those who move out of the state find that their certification as bilingual physicians helps them to locate in areas of their first choice. Their marketability increases and their fears of a physician surplus diminish.

The UCSD School of Medicine program is completing its second year, so it is too early to assess results. Its effectiveness can be assessed in part through the students' responses to the open enrollments. A full roster of applicants has appeared at the beginning of each year. Their consequent commitment to the classes is reflected in the steady attendance, minimal attrition and in their written comments. In addition, there is a consensus among students that this course is effective in preparing them for their third-year clinical clerkships. This impression has been corroborated by their receiving preferential treatment on the clinical services, being assigned more Latino patients and by being sought as interpreters when other students are confronted with Spanish-speaking patients.

The success of the program is also measured through evaluations written by the Latino preceptors when called upon to assess the oral proficiency of each individual student at the end of the academic year. In 1984-1985, all the students enrolled in the two-tiered course passed rigidly defined proficiency examinations.

The success of this program is further attested to by the actions of the Latino preceptors themselves. These physicians are volunteers who receive no remuneration for their teaching services and all have continued to participate in this program.

#### REFERENCES

1. Nydegger CN: Multiple causality: Consequences for medical practice (Cross-cultural Medicine). West J Med 1983; 138:430-436

2. Putsh R: Cross cultural communication. JAMA 1985; 245:3344-3348

3. Meleis AI, Jonsen AR: Ethical crises and cultural differences (Medicine in Perspective). West J Med 1983; 138:889-893

4. Starr P: The Social Transformation of American Medicine—The Rising of a Sovereign Profession and the Making of a Vast Industry. New York, Basic Books, 1983

5. Kristal L, Pennock P, Foote S, et al: Cross-cultural family medicine residency training. J Fam Pract 1983; 17:683-687

6. Krashen S, Terrel T: The Natural Approach. West Hayward, Calif, Alemany Press, 1983

7. Almeida J, Mohler SC, Stinson RR: Descubrir y Crear, 2nd Ed. New York, Harper & Row, 1981

8. Jarvis AC, Lebredo R: Spanish for Medical Personnel, 2nd Ed. Lexington, Mass, Heath & Co, 1980

9. Teed C, Raley H, Barber J: Conversational Spanish for the Medical and Health Professions. New York, Holt, Rinehart & Winston, 1983

10. Werner D: Donde No Hay Doctor: Una Guia Para los Campesinos Que Viven Lejos de los Centros Medicos. Palo Alto, Calif, Hesperian Foundation, 1981

11. Nassi RJ, Bernstein B, Nuzzi TF: Workbook in Spanish—Three Years. New York, Amsco School Publ, 1966

12. Williams S, Burgos-Sasscer R: Exploraciones Chicano-Riquenas. New York, Random House, 1981

13. Bowden CL, Burstein AG: Psychosocial Basis of Health Care. Baltimore, Williams & Wilkins, 1983

# Nailing Down the Cause of Periungual Lesions

HENRY SCHNEIDERMAN, MD, *and* ANN L. PARKE, MD, FRCP(C), *Farmington, Connecticut*

*An elderly woman had suffered the ravages of chronic nodular, erosive, seropositive rheumatoid arthritis for many years. She had received prolonged corticosteroid therapy for continuing active disease. A carbuncle of the left heel ultimately led to a left pyothorax and this in turn caused a staphylococcal bacteremia. Several days after bacteremia was documented and while she was receiving antimicrobics intravenously, an examiner noticed blackened areas near several fingernails (Figure 1). The patient was uncertain when these had first arisen. Although she was frail and systemically ill, there had been no episodes of shock nor of clinical ventilatory failure.*

**Figure 1.**—Black, nearly linear and slightly retracted lesions do not quite adjoin lateral borders of fingernail. Suture fragment appears proximally, at site of skin biopsy.

## Readers are invited to choose a diagnosis from the following differential diagnostic list.

- ☐ A. Periungual infarcts due to vasculitis.
- ☐ B. Skin necrosis associated with Raynaud's phenomenon (digital arterial vasospasm).
- ☐ C. Splinter hemorrhages relating to staphylococcal endocarditis.
- ☐ D. Janeway's lesions in atypical, periungual locations.
- ☐ E. Acral gangrene due to hypoperfusion.
- ☐ F. Necrotizing paronychial infection.

SEE FOLLOWING PAGE FOR DIAGNOSIS AND DISCUSSION.

(Schneiderman H, Parke AL: Nailing down the cause of periungual lesions. West J Med 1987 Apr; 146:505-506)

From the Departments of Pathology (Dr Schneiderman) and Medicine (Drs Schneiderman and Parke), University of Connecticut Health Center, Farmington, Connecticut. Dr Schneiderman is a Teaching and Research Scholar of the American College of Physicians.

Reprint requests to Henry Schneiderman, MD, Room CG-058, University of Connecticut Health Center, Farmington, CT 06032.

# Information

## Answer

The diagnosis is **A**, periungual infarcts due to vasculitis. In this case, destructive rheumatoid arthritis was accompanied by rheumatoid vasculitis. Digital skin damage, namely, ischemic necrosis, reflected arterial and arteriolar occlusion by the inflammatory, edematous and secondarily thrombotic lesions of vasculitis (Figure 2). Findings on biopsy in rheumatoid vasculitis vary considerably, probably relating both to the known patchy distribution of vasculitides and to the multiplicity of subtypes of rheumatoid vasculitis.[1] The site of biopsy of the skin of this patient's finger is marked by a suture fragment in Figure 1. The biopsy specimen showed a leukocytoclastic (hypersensitivity-type) vasculitic pattern, with infarction of skin supplied by affected vessels. Rheumatoid vasculitis typically occurs, as in this case, in aggressive seropositive, erosive disease. It is often associated with other extra-articular manifestations as well. It may produce small infarcts in the pulp space of the fingers or in periungual zones. Several other vasculitides can produce similar pathologic findings, but only lupus vasculitis shares the propensity to periungual infarcts.[1]

Iatrogenic (drug-induced) leukocytoclastic vasculitis can produce a similar histologic appearance in venules and capillaries, but rarely in this distribution around nails and on fingers. Severe Raynaud's phenomenon can cause necrosis, but this usually occurs on the pulp side, as does acral ("fingertip") gangrene due to any cause. Raynaud's phenomenon is more often a feature of progressive systemic sclerosis (scleroderma) than of ordinary rheumatoid arthritis.

Splinter hemorrhages are subungual rather than periungual. They seldom signify important systemic disease of blood, clotting, heart or vessels. Many cases are traumatic.[2]

Janeway's lesions may occasionally occur around nails rather than in their preferred locales, the palms and pulp surfaces, but they are erythematous, not necrotic. Like all the other cutaneous signs of endocarditis, they are immune, not embolic in origin[3] and, like these others, they have grown rare. Perhaps antibiotic treatment of infective endocarditides has contributed to their decline. Janeway's lesions require more time after the onset of illness to develop than was recorded in this case, presumably because the antigen must grow sufficiently abundant and the host response sufficiently pronounced before they are clinically visible.

Paronychia never leaves a clear zone, as here, immediately adjoining the nail. Also, paronychia does not progress to necrosis.

#### REFERENCES

1. Healey LA: Rheumatoid vasculitis, chap 20, *In* Utsinger PD, Zvaifler NJ, Ehrlich GE (Eds): Rheumatoid Arthritis: Etiology, Diagnosis, Management. Philadelphia, JB Lippincott, 1985, pp 351-355

2. Beaven DW, Brook SE: Color Atlas of the Nail in Clinical Diagnosis. Chicago Year Book Medical Publishers, 1984, pp 30, 132

3. Farrior JB III, Silverman ME: A consideration of the differences between a Janeway's lesion and an Osler's node in infectious endocarditis. Chest 1976; 70:239-243

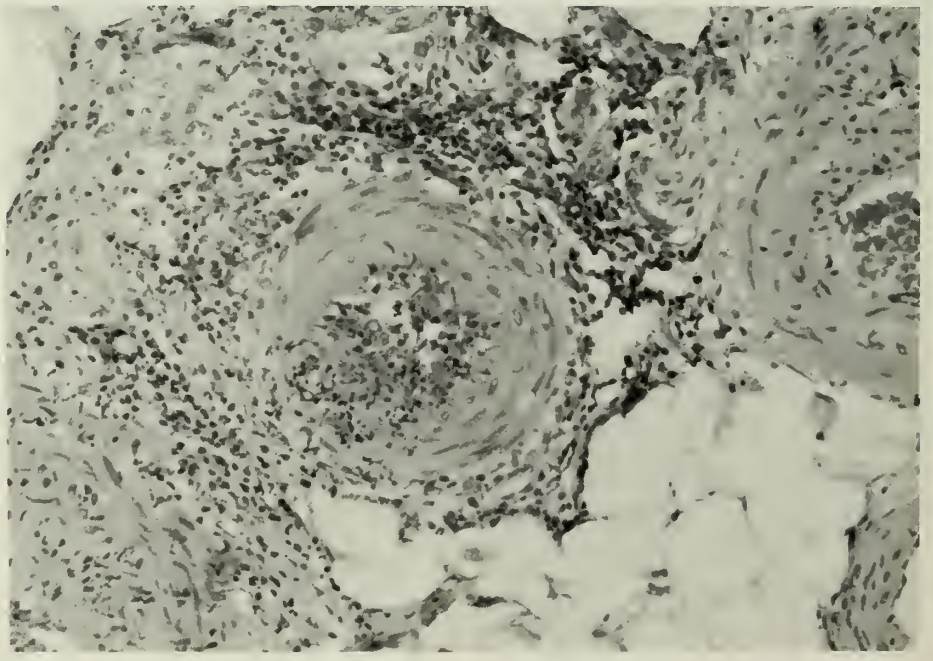


**Figure 2.**—Several histologic patterns of rheumatoid vasculitis have been reported. This severe example, from a muscle biopsy specimen in another case of rheumatoid arthritis, represents the extreme end of the spectrum. It shows fibrinoid necrosis in a small artery and pronounced inflammation. Thus, this subtype resembles polyarteritis nodosa (hematoxylin and eosin stain, original magnification ×200), whereas that of the case reported here resembles simple hypersensitivity (leukocytoclastic) vasculitis.

# *Significant reduction in angina attacks...*

- All-day, all-night protection
- Few CNS side effects*
- Once-a-day convenience

* The most commonly reported side effects, dizziness and fatigue, have been reported in approximately 2 of 100 patients receiving **CORGARD**.

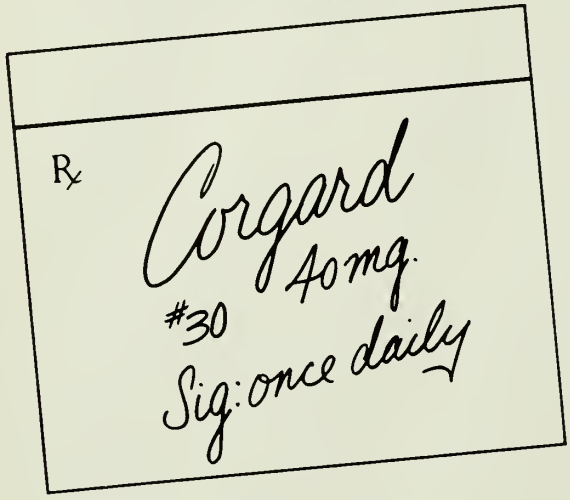
# CORGARD®
## (nadolol tablets)
## Advantages beyond control

For a complete discussion of **CONTRAINDICATIONS, PRECAUTIONS, ADVERSE REACTIONS, and WARNINGS,** including avoidance of abrupt withdrawal, please see brief summary on adjacent page.

NOW MEDI-CAL APPROVED

# CORGARD®
# (nadolol tablets)

## *Advantages beyond control for the angina patient*




**CORGARD® TABLETS**
**Nadolol Tablets**

**DESCRIPTION:** CORGARD (nadolol) is a synthetic non-selective beta-adrenergic receptor blocking agent.

**CONTRAINDICATIONS:** Bronchial asthma, sinus bradycardia and greater than first degree conduction block, cardiogenic shock, and overt cardiac failure (see WARNINGS).

**WARNINGS: Cardiac Failure**—Sympathetic stimulation may be a vital component supporting circulatory function in congestive heart failure, and its inhibition by beta-blockade may precipitate more severe failure. Although beta-blockers should be avoided in overt congestive heart failure, if necessary, they can be used with caution in patients with a history of failure who are well-compensated, usually with digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle. IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta-blockers can, in some cases, lead to cardiac failure; therefore, at first sign or symptom of heart failure, digitalize and/or give diuretics, and closely observe response, or discontinue nadolol (gradually if possible).

**Exacerbation of Ischemic Heart Disease Following Abrupt Withdrawal**—Hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred after *abrupt* discontinuation of such therapy. When discontinuing chronic use of nadolol, particularly in patients with ischemic heart disease, gradually reduce dosage over a 1- to 2- week period and carefully monitor the patient. Reinstitute nadolol promptly (at least temporarily) and take other measures appropriate for management of unstable angina if angina markedly worsens or acute coronary insufficiency develops. Warn patients not to interrupt or discontinue therapy without physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue nadolol therapy abruptly even in patients treated only for hypertension.

**Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema)**—PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA-BLOCKERS. Administer nadolol with caution since it may block bronchodilation produced by endogenous or exogenous catecholamine stimulation of beta$_2$ receptors.

**Major Surgery**—Because beta blockade impairs the ability of the heart to respond to reflex stimuli and may increase risks of general anesthesia and surgical procedures, resulting in protracted hypotension or low cardiac output, it has generally been suggested that such therapy should be withdrawn several days prior to surgery. Recognition of the increased sensitivity to catecholamines of patients recently withdrawn from beta-blocker therapy, however, has made this recommendation controversial. If possible, withdraw beta-blockers well before surgery takes place. In emergency surgery, inform the anesthesiologist that the patient is on beta-blocker therapy. Use of beta-receptor agonists such as isoproterenol, dopamine, dobutamine, or levarterenol can reverse the effects of nadolol. Difficulty in restarting and maintaining the heart beat has also been reported with beta-adrenergic receptor blocking agents.

**Diabetes and Hypoglycemia**—Beta-adrenergic blockade may prevent the appearance of premonitory signs and symptoms (e.g., tachycardia and blood pressure changes) of acute hypoglycemia. This is especially important with labile diabetics. Beta-blockade also reduces release of insulin in response to hyperglycemia; therefore, it may be necessary to adjust dose of antidiabetic drugs.

**Thyrotoxicosis**—Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. To avoid abrupt withdrawal of beta-adrenergic blockade which might precipitate a thyroid storm, carefully manage patients suspected of developing thyrotoxicosis.

**PRECAUTIONS: Impaired Renal Function**—Use nadolol with caution (see DOSAGE AND ADMINISTRATION section of package insert).

**Information for Patients**—Warn patients, especially those with evidence of coronary artery insufficiency, against interruption or discontinuation of nadolol without physician's advice. Although cardiac failure rarely occurs in properly selected patients, advise patients being treated with beta-adrenergic blocking agents to consult physician at first sign of impending failure. Advise patients in event of missed doses.

**Drug Interactions**—Concurrent administration may result in interactions with: Anesthetics, general—exaggeration of the hypotension induced by general anesthetics (see WARNINGS, Major Surgery). Antidiabetic drugs (oral agents and insulin)—hypoglycemia or hyperglycemia, adjust antidiabetic drug dosage accordingly (see WARNINGS, Diabetes and Hypoglycemia). Catecholamine-depleting drugs (e.g., reserpine)—additive effect, monitor closely for hypotension and/or excessive bradycardia

**Carcinogenesis, Mutagenesis, Impairment of Fertility**—In 1 to 2 years oral toxicologic studies in mice, rats, and dogs, nadolol did not produce significant toxic effects. In 2-year oral carcinogenic studies in rats and mice, nadolol did not produce neoplastic, preneoplastic, or nonneoplastic pathologic lesions.

**Pregnancy Category C**—In animal reproduction studies with nadolol, evidence of embryo- and fetotoxicity was found in rabbits (but not in rats or hamsters) at doses 5 to 10 times greater (on a mg/kg basis) than maximum indicated human dose; no teratogenic potential was seen in any of these species. There are no well-controlled studies in pregnant women; therefore, use nadolol in pregnant women only if potential benefit justifies potential risk to the fetus. Neonates of mothers who received nadolol at parturition have exhibited bradycardia, hypoglycemia and associated symptoms.

**Nursing Mothers**—Nadolol is excreted in human milk. Exercise caution when nadolol is administered to a nursing woman.

**Pediatric Use**—Safety and effectiveness in children have not been established.

**ADVERSE REACTIONS:** Most adverse effects have been mild and transient and have rarely required nadolol withdrawal.

**Cardiovascular**—Bradycardia with heart rates of less than 60 beats per minute occurs commonly, and heart rates below 40 beats per minute and/or symptomatic bradycardia were seen in about 2 of 100 patients. Symptoms of peripheral vascular insufficiency, usually of the Raynaud type, have occurred in approximately 2 of 100 patients. Cardiac failure, hypotension, and rhythm/conduction disturbances have each occurred in about 1 of 100 patients. Single instances of first degree and third degree heart block have been reported; intensification of AV block is a known effect of beta-blockers (see also CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS). **Central Nervous System**—Dizziness or fatigue reported in approximately 2 of 100 patients; paresthesias, sedation, and change in behavior reported in approximately 6 of 1000 patients. **Respiratory**—Bronchospasm reported in approximately 1 of 1000 patients (see CONTRAINDICATIONS and WARNINGS). **Gastrointestinal**—Nausea, diarrhea, abdominal discomfort, constipation, vomiting, indigestion, anorexia, bloating, and flatulence each reported in 1 to 5 of 1000 patients. **Miscellaneous**—Each of the following reported in 1 to 5 of 1000 patients: rash; pruritus; headache; dry mouth, eyes, or skin; impotence or decreased libido; facial swelling; weight gain; slurred speech; cough; nasal stuffiness; sweating; tinnitus; blurred vision; infrequent reversible alopecia.

The following adverse reactions have been reported in patients taking nadolol and/or other beta-adrenergic blocking agents, but no causal relationship to nadolol has been established. **Central Nervous System**—reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place; short-term memory loss, emotional lability with slightly clouded sensorium; decreased performance on neuropsychometrics. **Gastrointestinal**—mesenteric arterial thrombosis; ischemic colitis; elevated liver enzymes. **Hematologic**—agranulocytosis; thrombocytopenic or nonthrombocytopenic purpura. **Allergic**—fever combined with aching and sore throat; laryngospasm; respiratory distress. **Miscellaneous**—pemphigoid rash; hypertensive reaction in patients with pheochromocytoma; sleep disturbances; Peyronie's disease. The oculomucocutaneous syndrome associated with practolol has not been reported with nadolol.

**OVERDOSAGE:** Nadolol can be removed from the general circulation by hemodialysis. In addition to gastric lavage, employ the following measures as appropriate. In determining duration of corrective therapy, take note of long duration of effect of nadolol.

**Excessive Bradycardia**—Administer atropine (0.25 to 1.0 mg). If there is no response to vagal blockade, administer isoproterenol cautiously.

**Cardiac Failure**—Administer a digitalis glycoside and diuretic. It has been reported that glucagon may also be useful in this situation.

**Hypotension**—Administer vasopressors, e.g., epinephrine or levarterenol. (There is evidence that epinephrine may be the drug of choice.)

**Bronchospasm**—Administer a beta$_2$-stimulating agent and/or a theophylline derivative.

**DOSAGE**—For all patients, DOSAGE MUST BE INDIVIDUALIZED.

For **angina pectoris,** usual initial dose is 40 mg q.d.; may be gradually increased in 40 to 80 mg increments at 3 to 7 day intervals until optimum clinical response or pronounced slowing of the heart rate; usual maintenance dose is 40 or 80 mg q.d. (doses up to 160 or 240 mg daily may be needed). If treatment is to be discontinued, reduce dosage gradually over a period of 1 to 2 weeks (see WARNINGS).

For **hypertension,** usual initial dose is 40 mg q.d.; gradually increase in 40 to 80 mg increments until optimum blood pressure reduction is achieved, usual maintenance dose is 40 or 80 mg q.d. (doses up to 240 or 320 mg daily may be needed).

Patients with renal failure require adjustment in dosing interval; see package insert for dosage in these patients.

**For full prescribing information consult package insert.**

**HOW SUPPLIED:** In scored tablets containing 40, 80, 120, or 160 mg nadolol per tablet in bottles of 100 and in Unimatic® unit-dose packs of 100 tablets. The 40 mg, 80 mg, and 120 mg potencies are also available in bottles of 1000 tablets. (J3-527E)

PRINCETON PHARMACEUTICAL PRODUCTS
A SQUIBB COMPANY

© 1987 E. R. Squibb & Sons, Inc., Princeton, NJ

517-504 A

Issued: January 1987

CONTINUING MEDICAL EDUCATION

(Continued from Page 429)

May 2-3—**Automated Percutaneous Lumbar Discectomy Workshop.** UCSF at Hyatt Regency, San Francisco. Sat-Sun. Contact: UCSF.

May 4-6—**Osteoporosis Update—1987.** UCSF at Hyatt Regency, San Francisco. Mon-Wed. 18 hrs. $295. Contact: UCSF.

May 5-9—**7th Annual Diagnostic Ultrasound Post Conference Seminar.** Los Angeles Radiological Society at Sheraton Princeville Hotel, Kauai, Hawaii. Tues-Sat. 19 hrs. $395. Contact: Diane L. Johnson, LARS, 5200 Century Blvd, Ste 920, Los Angeles 90045. (213) 642-0921.

May 6-8—**Spine Update—1987.** UCSF at Hyatt on Union Square, San Francisco. Wed-Fri. 17 hrs. $295. Contact: UCSF.

June 10-13—**Advanced Echocardiography and Doppler Ultrasound—1987.** American College of Cardiology at Sheraton Harbor Island East, San Diego. Wed-Sat. Contact: Mary Anne McInerny, ACC, 9111 Old Georgetown Rd, Bethesda, MD 20814. (301) 897-5400, ext 226.

June 14-16—**1987 Radiology US Open Golf Meeting.** UCSF at Hyatt Regency, San Francisco. Sun-Tues. Contact: UCSF.

August 3-7—**Diagnostic Radiology Seminars.** UCSF at Hyatt Regency, Maui, Hawaii. Mon-Fri. 27.5 hrs. $495. Contact: UCSF.

August 13-15—**Advanced Ultrasound.** American College of Obstetricians and Gynecologists at Silverado Inn, Napa. Thurs-Sat. Contact: Robin Murray, ACOG, 600 Maryland Ave SW, Washington, DC 20024-2588. (202) 638-5577.

August 22-29—**Radiology.** USC at Maui Marriott Hotel, Maui, Hawaii. One week. 26 hrs. $525. Contact: USC.

August 26-28—**Interventional Radiology.** UCSF at Hyatt Regency Hotel, San Francisco. Wed-Fri. Contact: UCSF.

August 29-30—**Advances in Imaging Technology.** UCSF at Hyatt Regency, San Francisco. Sat-Sun. Contact: UCSF.

September 10-12—**Contemporary Diagnostic Imaging: CT, Interventional, MRI, US.** UCSF at Hyatt Regency, Monterey. Thurs-Sat. Contact: UCSF.

## SPORTS MEDICINE

July 27-31—**Sports Medicine Update—1987.** UCSD at San Diego Princess Hotel, Vacation Village. Mon-Fri. 29.5 hrs. $325. Contact: UCSD.

## SURGERY

April 30-May 2—**American Back Society Spring Symposium.** Anaheim Hilton Hotel. Thurs-Sat. Contact: Aubrey A. Swartz, American Back Soc, 2647 E. 14th St, Ste 401, Oakland 94601. (415) 536-9929.

April 30-May 2—**Postgraduate Course in General Surgery.** UCSF at Hotel Meridien, San Francisco. Thurs-Sat. 15 hrs. Contact: UCSF.

May 1-2—**Prosthetics/Orthotics.** UCD at Sacramento. Fri-Sat. Contact: UCD.

May 11-15—**The San Francisco Orthopaedic Review Course.** UCSF at San Francisco. Mon-Fri. 40 hrs. Contact: UCSF.

May 13—**Otolaryngology: ENT Infections.** LLU at LLU. Wed. 4 hrs. $60. Contact: LLU.

May 14-16—**Symposium on the Temporomandibular Joint.** UCSF at Hyatt Regency, Monterey. Thurs-Sat. 13 hrs. $295. Contact: UCSF.

May 18-21—**Cochlear Implant Training—1987.** House Ear Institute, Los Angeles. Mon-Thurs. 24 hrs. $250. Contact: Antonio De la Cruz, MD, House Ear Institute, 256 S Lake St, Los Angeles 90057. (213) 483-4431.

June 4-5—**16th Annual Neurosurgical Postgraduate Course.** UCSF at San Francisco. Thurs-Sat. 15 hrs. Contact: UCSF.

June 5-6—**6th Annual Southwestern Regional Cutaneous Flap Workshop.** UCLA at UCLA. Fri-Sat. 11 hrs. Contact: UCLA.

June 14-20—**Temporal Bone Surgical Dissection—1987.** House Ear Institute, Los Angeles. Sun-Sat. 62 hrs. $950. Contact: Antonio De la Cruz, MD, House Ear Institute, 256 S Lake St, Los Angeles 90057. (213) 483-4431.

September 14-17—**Cochlear Implant Training—1987.** House Ear Institute, Los Angeles. Mon-Thurs. 24 hrs. $250. Contact: Antonio De la Cruz, MD, House Ear Institute, 256 S Lake St, Los Angeles 90057. (213) 483-4431.

## OF INTEREST TO ALL PHYSICIANS

April 18-22—**Physical Diagnosis: An Intensive Review.** Memorial Medical Center of Long Beach at Maui, Hawaii. Sat-Wed. 28 hrs. Contact: Beverly Ritchie, Memorial Medical Center of Long Beach, 2801 Atlantic Ave, PO Box 1428, Long Beach 90801-1428. (213) 595-2311.

April 20-23—**Selective Topics in Dermatology and Pulmonary Intensive Care.** LLU at LLU. Mon-Thurs. 16 hrs. $400. Contact: LLU.

April 23-25—**37th Annual Regional Postgraduate Institute for San Joaquin Valley Counties.** CMA and Fresno-Madera Medical Society at Curry Village Pavilion, Yosemite. Thurs-Sat. 12 hrs. $150-200. Contact: Janice Rigney, CMA.

April 24-25—**Sex, Drugs and Rock'n Roll: Effects on the Family.** UCI at Sheraton Newport, Newport Beach. Fri-Sat. 13.5 hrs. $175. Contact: UCI.

April 25—**Patient Education: Neuromuscular Disease.** UCD at Pacific Bell Auditorium, Sacramento. Sat. Contact: UCD.

April 25-26—**Transurethral Ureteroscopy: A Seminar and Workshop.** UCSD at La Jolla Marriott Hotel, La Jolla. Sat-Sun. 13.5 hrs. $275-400. Contact: UCSD.

May 11-12—**Annual Child Abuse Conference—Physical Abuse: The Traumatized Child and Family.** UCD at Sacramento Inn. Mon-Tues. 10 hrs. Contact: UCD.

May 11-13—**Arthritis Update '87.** Sharp Memorial Hospital, San Diego and UCSD at Hyatt Islandia Hotel, San Diego. Mon-Wed. Contact: Mary Belich, Sharp Memorial Hospital, 7901 Frost St, San Diego 92123-2788. (619) 541-3400.

May 13—**Modern Use of Antihiotics.** UCD at Red Lion Motor Inn. Wed. 4 hrs. Contact: UCD.

May 15-16—**Issues in Identification, Amplification and Rehabilitation With the Hard of Hearing, School-Aged Child.** UCI. Fri-Sat. 10 hrs. Contact: UCI.

May 20-23—**Physical Diagnosis: An Intensive Review.** Memorial Medical Center of Long Beach at Long Beach. Wed-Sat. 28 hrs. Contact: Beverly Ritchie, Memorial Medical Center of Long Beach, 2801 Atlantic Ave, PO Box 1428, Long Beach 90801-1428. (213) 595-2311.

June 8-13—**UCI Family Practice Refresher Course.** UCI at Newport Beach. Mon-Sat. Contact: UCI.

June 11—**AIDS: Issues for the Primary Care Physician.** Alta Bates Hospital, Berkeley. Thurs. 5 hrs. $40. Contact: Mary Grim, Alta Bates Hospital, 3001 Colby St, Berkeley 94705. (415) 540-1420.

June 14-19—**Fingers to the Toes: Orthopaedics for Primary Care.** UCD at Stanford Sierra Camp, Fallen Leaf Lake. Sun-Fri. 36 hrs. Contact: UCD.

June 15-19—**Sexually Transmitted Disease (STD) Clinician Training Course—Advanced.** Long Beach Health Dept at Long Beach. Mon-Fri. Contact: Anne-Renee Heningberg, Long Beach STD Trng Ctr, PO Box 6157, Long Beach 90806. (213) 427-7421.

June 19-21—**Family Practice Update.** USC at Pasadena Hilton Hotel, Pasadena. Fri-Sun. 16 hrs. $250. Contact: USC.

June 26—**Mucosal Injury, Esophageal Dysfunction, and Sleep Disorders.** Sequoia Hospital District, Redwood City. Fri. 7 hrs. $110. Contact: Daniel Liebowitz, MD, Sequoia Hospital, Whipple and Alameda, Redwood City 94062. (800) 345-0409.

June 28-29—**9th Annual Poison Control Center: Management of Drug Overdose and Poisoning.** UCSF at San Francisco. Sun-Mon. 14 hrs. $235. Contact: UCSF.

June 28-July 2—**Advances in Primary Care: 14th Annual Family Practice Refresher Course.** UCD at Caesar's Tahoe, So Lake Tahoe. Sun-Thurs. Contact: UCD.

July 6-9—**Family Practice Board Review.** UCSF at UCSF. Mon-Thurs. 25 hrs. $375. Contact: UCSF.

August 16-26—**30th Anniversary Postgraduate Refresher Course—Program I.** USC at Sheraton Waikiki Hotel, Honolulu and the Marriott Hotel, Maui, Hawaii. Sun-Wed. 37 hrs. $535-585. Contact: USC, in California, (800) 321-1919, outside California, (800) 421-6729.

August 20-21—**6th Annual: General Medicine Update for Practicing Physicians.** Northern Inyo Hospital, Bishop. Wed-Thurs. 10 hrs. Contact: Lynda Schmidt, Northern Inyo Hosptial, 150 Pioneer Lane, Bishop 93514. (619) 873-5811.

(Continued on Page 510)

CONTINUING MEDICAL EDUCATION

(Continued from Page 509)

August 23-September 2—**30th Anniversary Postgraduate Refresher Course—Program II.** USC at Marriott Hotel, Maui and the Waiohai Hotel, Kaui, Hawaii. Sun-Wed. 37 hrs. $535-585. Contact: USC, in California, (800) 321-1929, outside California, (800) 421-6729.

September 9-11—**Primary Care Medicine: Principles and Practice.** UCSF at Hyatt on Union Square, San Francisco. Wed-Fri. $365. Contact: UCSF.

September 14-18—**STD Clinician Training Course—Intensive.** Long Beach Health Dept. Mon-Fri. Contact: Anne-Renee Heningberg, Long Beach STD Training Center, PO Box 6157, Long Beach 90806. (213) 427-7421.

September 21-22—**7th Annual Bristol-Myers Symposium on Nutrition Research: Nutrition and the Origins of Disease.** UCD at Fairmont Hotel, San Francisco. Mon-Tues. Contact: UCD.

## IDAHO

June 28-July 5—**Effective Management of Common Sports Injuries.** Middle Fork of the Salmon River. One week. Sponsored by the University of Arizona College of Medicine, Department of Family and Community Medicine, and Epic Expeditions. 24 hrs. Contact: Kathy Rairigh, EPIC EXPEDITIONS, PO Box 209, Sun Valley, ID 83353. (208) 788-4995.

July 27-August 2—**Idaho Medical Association Annual Meeting.** Coeur d'Alene. One week. Contact: IMA, 305 W Jefferson, PO Box 2668, Boise 83701. (208) 344-7888.

August 1-8—**Forefronts in Pediatrics.** Sun Valley. One week. Sponsored by the University of Arizona College of Medicine, Department of Family and Community Medicine, and Epic Expeditions. 24 hrs. Contact: Kathy Rairigh, EPIC EXPEDITIONS, PO Box 209, Sun Valley, ID 83353. (208) 788-4995.

## MONTANA

June 18-20—**Montana Academy of Family Physicians—Annual Meeting.** Fairmont Hot Springs, Anaconda. 17 hrs. Contact: John Patterson, MD, 7 E Beall, Bozeman 59715. (406) 587-5123.

## NEW MEXICO

Information, requests for accreditation and items to be listed should be sent to the chairman of the CME Committee, New Mexico Medical Society, 303 San Mateo NE, Suite 204, Albuquerque, NM 87108 at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 266-7868.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

April 24-25—**Practical Orthopaedics in the Primary Care Setting.** Albuquerque. Fri-Sat. Veterans Administration Medical Center. Contact: Office of CME, UNM School of Medicine, Albuquerque 87131. (505) 277-3942.

May 6-8—**New Mexico Medical Society—Annual Meeting.** Albuquerque. Wed-Fri. Clarion Four Seasons. Contact: NMMS, 303 San Mateo NE, #204, Albuquerque 87108. (505) 266-7868.

May 15-16—**Biological and Ethical Dimensions of Human Transplantation.** Albuquerque. Fri-Sat. Contact: Office of Medical Education, Presbyterian Hospital, PO Box 26666, Albuquerque 87125. (505) 841-1225.

## UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the CME office of the Utah State Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. They also must meet the definition of Utah Approved CME Credit for the purpose of medical license reregistration in Utah. Accredited institutions wishing to list AMA Category 1/Utah Approved CME courses here should send information at least two months in advance to the Office of Continuing Medical Education, 540 East Fifth South, Salt Lake City, Utah 84102; or phone (801) 355-5290. For information on CME accreditation or on the CME requirements of the Utah Physicians' Licensing Board, please write the CME office at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution or the CME office for current details.

### MEDICAL GRAND ROUNDS

Each Wed—8:00-9:00 a.m. Alternating between University of Utah Medical Center and VA Medical Center, Salt Lake City. Contact: William D. Odell, MD, PhD, Professor and Chairman, Dept of Internal Medicine, Univ of Utah, (801) 581-7606.

* * *

April 23-24—**Contemporary Adolescent Health** (Sponsor: UUMC). Thurs-Fri. Marriott Hotel, Salt Lake City. Contact: Valerie Velez, (801) 359-2444.

May 11-15—**Industrial Toxicology** (Sponsor: UUMC). Mon-Fri. Univ of Utah, Salt Lake City. 28.5 hrs. Contact: (801) 581-5710.

#### SPONSORS OF COURSES—ABBREVIATIONS

AHA: American Heart Association, Utah Affiliate, 645 E 400 South, Salt Lake City 84102. (801) 322-5601.

BYUHS: Brigham Young University Health Services, McDonald Student Health Center, Brigham Young University, Provo 84602. (801) 378-2771.

CH: Castleview Hospital (formerly Carbon Hospital), RFD 2, Box 46, Price 84501. (801) 637-4800.

CWH: Cottonwood Hospital, 5770 S 300 East, Salt Lake City 84101. (801) 262-3461.

DMC: Dixie Medical Center, 544 S 400 East, St George 84770. (801) 673-9681.

HCH: Holy Cross Hospital, 1045 E First South, Salt Lake City 84102. (801) 350-4744.

ITS: Intermountain Thoracic Society, 1616 S 11th East, Salt Lake City 84105. (801) 484-4456.

LDSH: Latter-Day Saints Hospital, 325 8th Ave, Salt Lake City 84143. (801) 350-1100.

LRH: Logan Regional Hospital, 1400 N 5th East, Logan 84321. (801) 752-2050.

MDH: McKay-Dee Hospital Center, 3939 Harrison Blvd, Ogden 84409. (801) 399-4141.

MVH: Mountain View Hospital, 1000 E Highway 6, Payson 84651. (801) 465-9201.

(Continued on Page 520)

# DEPAKOTE®

## DIVALPROEX SODIUM ENTERIC-COATED TABLETS

**All the advantages of Depakene® (valproic acid) plus improved gastrointestinal tolerance**

# NOW ON MEDI-CAL FORMULARY

Medi-Cal Numbers:

(Actual size)

500 mg

**2414D**
**500 mg**

(Actual size)

250 mg

**2414A**
**250 mg**

(Actual size)

125 mg

NO. PENDING
**125 mg**

Please see adjoining page for prescribing information.

Abbott Laboratories, North Chicago, IL60064

# DEPAKOTE®

## DIVALPROEX SODIUM
## ENTERIC-COATED TABLETS

## NOW ON MEDI-CAL FORMULARY

**WARNING**

HEPATIC FAILURE RESULTING IN FATALITIES HAS OCCURRED IN PATIENTS RECEIVING VALPROIC ACID AND ITS DERIVATIVES. EXPERIENCE HAS INDICATED THAT CHILDREN UNDER THE AGE OF TWO YEARS ARE AT A CONSIDERABLY INCREASED RISK OF DEVELOPING FATAL HEPATOTOXICITY, ESPECIALLY THOSE ON MULTIPLE ANTICONVULSANTS, THOSE WITH CONGENITAL METABOLIC DISORDERS, THOSE WITH SEVERE SEIZURE DISORDERS ACCOMPANIED BY MENTAL RETARDATION, AND THOSE WITH ORGANIC BRAIN DISEASE. WHEN DEPAKOTE IS USED IN THIS PATIENT GROUP, IT SHOULD BE USED WITH EXTREME CAUTION AND AS A SOLE AGENT. THE BENEFITS OF SEIZURE CONTROL SHOULD BE WEIGHED AGAINST THE RISKS. ABOVE THIS AGE GROUP, EXPERIENCE HAS INDICATED THAT THE INCIDENCE OF FATAL HEPATOTOXICITY DECREASES CONSIDERABLY. IN PROGRESSIVELY OLDER PATIENT GROUPS.

THESE INCIDENTS USUALLY HAVE OCCURRED DURING THE FIRST SIX MONTHS OF TREATMENT. SERIOUS OR FATAL HEPATOTOXICITY MAY BE PRECEDED BY NON-SPECIFIC SYMPTOMS, SUCH AS LOSS OF SEIZURE CONTROL, MALAISE, WEAKNESS, LETHARGY, FACIAL EDEMA, ANOREXIA AND VOMITING. PATIENTS SHOULD BE MONITORED CLOSELY FOR APPEARANCE OF THESE SYMPTOMS. LIVER FUNCTION TESTS SHOULD BE PERFORMED PRIOR TO THERAPY AND AT FREQUENT INTERVALS THEREAFTER, ESPECIALLY DURING THE FIRST SIX MONTHS.

**DESCRIPTION**. Divalproex sodium is a stable coordination compound comprised of sodium valproate and valproic acid in a 1:1 molar relationship and formed during the partial neutralization of valproic acid with 0.5 equivalent of sodium hydroxide. Chemically it is designated as sodium hydrogen bis(2-propylpentanoate).

Divalproex sodium has a molecular weight of 310.41 and occurs as a white powder with a characteristic odor.

DEPAKOTE is an oral antiepileptic supplied as enteric coated tablets in three dosage strengths containing divalproex sodium equivalent to 125 mg, 250 mg or 500 mg of valproic acid.

**Inactive Ingredients**

125 mg tablets: cellulosic polymers, diacetylated monoglycerides, FD&C Blue No. 1, FD&C Red No. 40, povidone, pregelatinized starch (contains corn starch), silica gel, talc, titanium dioxide, vanillin and other ingredients.

250 mg tablets: cellulosic polymers, diacetylated monoglycerides, FD&C Yellow No. 6, iron oxide, povidone, pregelatinized starch (contains corn starch), silica gel, talc, titanium dioxide, vanillin and other ingredients.

500 mg tablets: cellulosic polymers, diacetylated monoglycerides, D&C Red No. 30, FD&C Blue No. 2, iron oxide, povidone, pregelatinized starch (contains corn starch), silica gel, talc, titanium dioxide, vanillin and other ingredients.

**CLINICAL PHARMACOLOGY**. DEPAKOTE is an antiepileptic agent which is chemically related to valproic acid. It has no nitrogen or aromatic moiety characteristic of other antiepileptic drugs. The mechanism by which DEPAKOTE exerts its antiepileptic effects has not been established. It has been suggested that its activity is related to increased brain levels of gamma aminobutyric acid (GABA). The effect on the neuronal membrane is unknown. DEPAKOTE dissociates into valproate in the gastrointestinal tract.

Because of the enteric coating of DEPAKOTE, absorption is delayed one hour following oral administration. Thereafter, DEPAKOTE is uniformly and reliably absorbed, as shown by studies in normal volunteers. Peak serum levels of valproate occur in 3 to 4 hours. Bioavailability of divalproex sodium tablets was found to be equivalent to that of DEPAKENE™ (valproic acid) capsules. Concomitant administration with food would be expected to slow absorption but not affect the extent of absorption. The serum half-life of valproate is typically in the range of six to sixteen hours. Half-lives in the lower part of the above range are usually found in patients taking other antiepileptic drugs capable of enzyme induction.

Enteric coated divalproex sodium may reduce the incidence of the irritative gastrointestinal effects of valproate as compared to valproic acid capsules.

Valproate is rapidly distributed and at therapeutic drug concentrations, drug is highly bound (90%) to human plasma proteins. Increases in dose may result in decreases in the extent of protein binding and increased valproate clearance and elimination.

Elimination of DEPAKOTE and its metabolites occurs principally in the urine, with minor amounts in the feces and expired air. Very little unmetabolized parent drug is excreted in the urine. The drug is primarily metabolized in the liver and is excreted as the glucuronide conjugate. Other metabolites in the urine are products of beta-, omega-1 and omega-oxidation (C-3, C-4 and C-5 positions). The major oxidative metabolite in the urine is 2-propyl-3-keto-pentanoic acid; minor metabolites are 2-propyl-glutaric acid, 2-propyl-5-hydroxypentanoic acid, 2-propyl-3-hydroxypentanoic acid and 2-propyl-4-hydroxypentanoic acid.

**INDICATIONS AND USAGE**. DEPAKOTE (divalproex sodium) is indicated for use as sole and adjunctive therapy in the treatment of simple (petit mal) and complex absence seizures. DEPAKOTE may also be used adjunctively in patients with multiple seizure types which include absence seizures.

In accordance with the International Classification of Seizures, simple absence is defined as very brief clouding of the sensorium or loss of consciousness (lasting usually 2-15 seconds), accompanied by certain generalized epileptic discharges without other detectable clinical signs. Complex absence is the term used when other signs are also present.

SEE "WARNINGS" SECTION FOR STATEMENT REGARDING FATAL HEPATIC DYSFUNCTION.

**CONTRAINDICATIONS**. DEPAKOTE (DIVALPROEX SODIUM) SHOULD NOT BE ADMINISTERED TO PATIENTS WITH HEPATIC DISEASE OR SIGNIFICANT DYSFUNCTION.

DEPAKOTE is contraindicated in patients with known hypersensitivity to the drug.

**WARNINGS**. **Hepatic failure resulting in fatalities has occurred in patients receiving valproic acid. These incidents usually have occurred during the first six months of treatment. Serious or fatal hepatotoxicity may be preceded by non-specific symptoms such as loss of seizure control, malaise, weakness, lethargy, facial edema, anorexia and vomiting. Patients should be monitored closely for appearance of these symptoms. Liver function tests should be performed prior to therapy and at frequent intervals thereafter, especially during the first six months. However, physicians should not rely totally on serum biochemistry since these tests may not be abnormal in all instances, but should also consider the results of careful interim medical history and physical examination. Caution should be observed when administering DEPAKOTE to patients with a prior history of hepatic disease. Patients on multiple anticonvulsants, children, those with congenital metabolic disorders, those with severe seizure disorders accompanied by mental retardation, and those with organic brain disease may be at particular risk. Experience has indicated that children under the age of two years are at a considerably increased risk of developing fatal hepatotoxicity, especially those with the aforementioned conditions. When DEPAKOTE is used in this patient group, it should be used with extreme caution and as a sole agent. The benefits of seizure control should be weighed against the risks. Above this age group, experience has indicated that the incidence of fatal hepatotoxicity decreases considerably in progressively older patient groups.**

**The drug should be discontinued immediately in the presence of significant hepatic dysfunction, suspected or apparent. In some cases, hepatic dysfunction has progressed in spite of discontinuation of drug.**

The frequency of adverse effects (particularly elevated liver enzymes) may be dose-related. The benefit of improved seizure control which may accompany the higher doses should therefore be weighed against the possibility of a greater incidence of adverse effects.

*Usage in Pregnancy*. ACCORDING TO PUBLISHED AND UNPUBLISHED REPORTS, VALPROIC ACID MAY PRODUCE TERATOGENIC EFFECTS IN THE OFFSPRING OF HUMAN FEMALES RECEIVING THE DRUG DURING PREGNANCY.

THERE ARE MULTIPLE REPORTS IN THE CLINICAL LITERATURE WHICH INDICATE THAT THE USE OF ANTIEPILEPTIC DRUGS DURING PREGNANCY RESULTS IN AN INCREASED INCIDENCE OF BIRTH DEFECTS IN THE OFFSPRING. ALTHOUGH DATA ARE MORE EXTENSIVE WITH RESPECT TO TRIMETHADIONE, PARAMETHADIONE, PHENYTOIN AND PHENOBARBITAL, REPORTS INDICATE A POSSIBLE SIMILAR ASSOCIATION WITH THE USE OF OTHER ANTIEPILEPTIC DRUGS. THEREFORE, ANTIEPILEPTIC DRUGS SHOULD BE ADMINISTERED TO WOMEN OF CHILDBEARING POTENTIAL ONLY IF THEY ARE CLEARLY SHOWN TO BE ESSENTIAL IN THE MANAGEMENT OF THEIR SEIZURES.

THE INCIDENCE OF NEURAL TUBE DEFECTS IN THE FETUS MAY BE INCREASED IN MOTHERS RECEIVING VALPRODATE DURING THE FIRST TRIMESTER OF PREGNANCY. THE CENTERS FOR DISEASE CONTROL (CDC) HAS ESTIMATED THE RISK OF VALPROIC ACID EXPOSED WOMEN HAVING CHILDREN WITH SPINA BIFIDA TO BE APPROXIMATELY 1 TO 2%.[1] THIS RISK IS SIMILAR TO THAT FOR NONEPILEPTIC WOMEN WHO HAVE HAD CHILDREN WITH NEURAL TUBE DEFECTS (ANENCEPHALY AND SPINA BIFIDA).

ANIMAL STUDIES ALSO HAVE DEMONSTRATED VALPROIC ACID INDUCED TERATOGENICITY. Studies in rats and human females demonstrated placental transfer of the drug. Doses greater than 65 mg/kg/day given to pregnant rats and mice produced skeletal abnormalities in the offspring, primarily involving ribs and vertebrae; doses greater than 150 mg/kg/day given to pregnant rabbits produced fetal resorptions and (primarily) soft tissue abnormalities in the offspring. In rats a dose-related delay in the onset of parturition was noted. Postnatal growth and survival of the progeny were adversely affected, particularly when drug administration spanned the entire gestation and early lactation period.

Antiepileptic drugs should not be discontinued in patients in whom the drug is administered to prevent major seizures because of the strong possibility of precipitating status epilepticus with attendant hypoxia and threat to life. In individual cases where the severity and frequency of the seizure disorder are such that the removal of medication does not pose a serious threat to the patient, discontinuation of the drug may be considered prior to and during pregnancy, although it cannot be said with any confidence that even minor seizures do not pose some hazard to the developing embryo or fetus.

The prescribing physician will wish to weigh these considerations in treating or counseling epileptic women of childbearing potential.

**PRECAUTIONS**. *Hepatic Dysfunction*. See "Boxed Warning", "Contraindications" and "Warnings" sections.

*General*. Because of reports of thrombocytopenia, inhibition of the secondary phase of platelet aggregation and abnormal coagulation parameters, platelet counts and coagulation tests are recommended before initiating therapy and at periodic intervals. It is recommended that patients receiving DEPAKOTE (divalproex sodium) be monitored for platelet count and coagulation parameters prior to planned surgery. Evidence of hemorrhage, bruising or a disorder of hemostasis/coagulation is an indication for reduction of DEPAKOTE dosage or withdrawal of therapy.

Hyperammonemia with or without lethargy or coma has been reported and may be present in the absence of abnormal liver function tests. If clinically significant elevation occurs, DEPAKOTE should be discontinued.

Since DEPAKOTE (divalproex sodium) may interact with concurrently administered antiepileptic drugs, periodic serum level determinations of concomitant antiepileptic drugs are recommended during the early course of therapy. (See "Drug Interactions" section.)

Valproate is partially eliminated in the urine as a keto metabolite which may lead to a false interpretation of the urine ketone test. There have been reports of altered thyroid function tests associated with valproate. The clinical significance of these is unknown.

*Information for Patients*. Since DEPAKOTE may produce CNS depression, especially when combined with another CNS depressant (e.g., alcohol), patients should be advised not to engage in hazardous occupations, such as driving an automobile or operating dangerous machinery, until it is known that they do not become drowsy from the drug.

*Drug Interactions*. Valproic acid may potentiate the CNS depressant activity of alcohol.

The concomitant administration of valproic acid with drugs that exhibit extensive protein binding (e.g., aspirin, carbamazepine and dicumarol) may result in alteration of serum drug levels.

THERE IS EVIDENCE THAT VALPROIC ACID CAN CAUSE AN INCREASE IN SERUM PHENOBARBITAL LEVELS BY IMPAIRMENT OF NON-RENAL CLEARANCE. THIS PHENOMENON CAN RESULT IN SEVERE CNS DEPRESSION. THE COMBINATION OF VALPROIC ACID AND PHENOBARBITAL HAS ALSO BEEN REPORTED TO PRODUCE CNS DEPRESSION WITHOUT SIGNIFICANT ELEVATIONS OF BARBITURATE OR VALPROATE SERUM LEVELS. ALL PATIENTS RECEIVING CONCOMITANT BARBITURATE THERAPY SHOULD BE CLOSELY MONITORED FOR NEUROLOGICAL TOXICITY. SERUM BARBITURATE LEVELS SHOULD BE OBTAINED, IF POSSIBLE, AND THE BARBITURATE DOSAGE DECREASED, IF APPROPRIATE.

Primidone is metabolized into a barbiturate and, therefore, may also be involved in a similar or identical interaction.

THERE HAVE BEEN REPORTS OF BREAKTHROUGH SEIZURES OCCURRING WITH THE COMBINATION OF VALPROIC ACID AND PHENYTOIN. MOST REPORTS HAVE NOTED A DECREASE IN TOTAL PLASMA PHENYTOIN CONCENTRATION. HOWEVER, INCREASES IN TOTAL PHENYTOIN SERUM CONCENTRATION HAVE BEEN REPORTED. AN INITIAL FALL IN TOTAL PHENYTOIN LEVELS WITH SUBSEQUENT INCREASE IN PHENYTOIN LEVELS HAS ALSO BEEN REPORTED. IN ADDITION, A DECREASE IN TOTAL SERUM PHENYTOIN, WITH AN INCREASE IN THE FREE VS. PROTEIN BOUND PHENYTOIN LEVELS, HAS BEEN REPORTED. THE DOSAGE OF PHENYTOIN SHOULD BE ADJUSTED AS REQUIRED BY THE CLINICAL SITUATION.

THE CONCOMITANT USE OF VALPROIC ACID AND CLONAZEPAM MAY PRODUCE ABSENCE STATUS.

There is inconclusive evidence regarding the effect of valproate on serum ethosuximide levels. Patients receiving valproate and ethosuximide especially along with other anticonvulsants, should be monitored for alterations in serum concentrations of both drugs.

Caution is recommended when DEPAKOTE (divalproex sodium) is administered with drugs affecting coagulation, e.g., aspirin and warfarin. (See "Adverse Reactions" section.)

*Carcinogenesis*. Valproic acid was administered to Sprague-Dawley rats and ICR (HA/ICR) mice at doses of 0, 80 and 170 mg/kg/day for two years. Although a variety of neoplasms were observed in both species, the chief findings were a statistically significant increase in the incidence of subcutaneous fibrosarcomas in high dose male rats receiving valproic acid and a statistically significant dose-related trend for benign pulmonary adenomas in male mice receiving valproic acid. The significance of these findings for man is unknown at present.

*Mutagenesis*. Studies on valproic acid have been performed using bacterial and mammalian systems. These studies have provided no evidence of a mutagenic potential for DEPAKOTE.

*Fertility*. Chronic toxicity studies in juvenile and adult rats and dogs demonstrated reduced spermatogenesis and testicular atrophy at doses greater than 200 mg/kg/day in rats and greater than 90 mg/kg/day in dogs. Segment I fertility studies in rats have shown doses up to 350 mg/kg/day for 60 days to have no effect on fertility. THE EFFECT OF DEPAKOTE (DIVALPROEX SODIUM) ON THE DEVELOPMENT OF THE TESTES AND ON SPERM PRODUCTION AND FERTILITY IN HUMANS IS UNKNOWN.

*Pregnancy*. Pregnancy Category D. See "Warnings" section.

*Nursing Mothers*. Valproate is excreted in breast milk. Concentrations in breast milk have been reported to be 1-10% of serum concentrations. It is not known what effect this would have on a nursing infant. Caution should be exercised when DEPAKOTE is administered to a nursing woman.

**ADVERSE REACTIONS**. Since valproic acid and its derivatives have usually been used with other antiepileptic drugs, it is not possible in most cases to determine whether the following adverse reactions can be ascribed to valproic acid alone or the combination of drugs.

*Gastrointestinal*. The most commonly reported side effects at the initiation of therapy are nausea, vomiting and indigestion. These effects are usually transient and rarely require discontinuation of therapy. Diarrhea, abdominal cramps and constipation have been reported. Both anorexia with some weight loss and increased appetite with weight gain have also been reported. The administration of enteric-coated divalproex sodium may result in reduction of gastrointestinal side effects in some patients.[2]

*CNS Effects*. Sedative effects have been noted in patients receiving valproic acid alone but are found most often in patients receiving combination therapy. Sedation usually disappears upon reduction of other antiepileptic medication. Tremor has been reported in patients receiving valproate and may be dose related. Ataxia, headache, nystagmus, diplopia, asterixis, spots before eyes, dysarthria, dizziness and incoordination have rarely been noted. Rare cases of coma have been noted in patients receiving valproic acid alone or in conjunction with phenobarbital.

*Dermatologic*. Transient increases in hair loss have been observed. Skin rash and erythema multiforme rarely have been noted.

*Psychiatric*. Emotional upset, depression, psychosis, aggression, hyperactivity and behavioral deterioration have been reported.

*Musculoskeletal*. Weakness has been reported.

*Hematologic*. Thrombocytopenia has been reported. Valproic acid inhibits the secondary phase of platelet aggregation. (See "Drug Interactions" section.) This may be reflected in altered bleeding time. Petechiae, bruising, hematoma formation, and frank hemorrhage have been reported. (See "Precautions" section.) Relative lymphocytosis and hypofibrinogenemia have been noted. Leukopenia and eosinophilia have also been reported. Anemia and bone marrow suppression have been reported.

*Hepatic*. Minor elevations of transaminases (e.g., SGOT and SGPT) and LDH are frequent and appear to be dose related. Occasionally, laboratory test results include, as well, increases in serum bilirubin and abnormal changes in other liver function tests. These results may reflect potentially serious hepatotoxicity. (See "Warnings" section.)

*Endocrine*. There have been reports of irregular menses and secondary amenorrhea, and rare reports of breast enlargement and galactorrhea occurring in patients receiving valproic acid and its derivatives.

Abnormal thyroid function tests have been reported. (See "Precautions" section.)

*Pancreatic*. There have been reports of acute pancreatitis, including rare fatal cases, occurring in patients receiving valproic acid and its derivatives.

*Metabolic*. Hyperammonemia. (See "Precautions" section.)

Hyperglycinemia has been reported and has been associated with a fatal outcome in a patient with preexistent nonketotic hyperglycinemia.

*Other*. Edema of the extremities has been reported.

**OVERDOSAGE**. Overdosage with valproic acid may result in deep coma.

Since DEPAKOTE tablets are enteric-coated, the benefit of gastric lavage or emesis will vary with the time since ingestion. General supportive measures should be applied with particular attention being given to the maintenance of adequate urinary output.

Naloxone has been reported to reverse the CNS depressant effects of valproate overdosage. Because naloxone could theoretically also reverse the antiepileptic effects of DEPAKOTE, it should be used with caution.

**DOSAGE AND ADMINISTRATION**. DEPAKOTE is administered orally. The recommended initial dose is 15 mg/kg/day, increasing at one week intervals by 5 to 10 mg/kg/day until seizures are controlled or side effects preclude further increases. The maximum recommended dosage is 60 mg/kg/day. If the total daily dose exceeds 250 mg, it should be given in a divided regimen.

*Conversion from DEPAKENE to DEPAKOTE*. In patients previously receiving DEPAKENE (valproic acid) therapy, DEPAKOTE should be initiated at the same total daily dose and dosing schedule.[3] After the patient is stabilized on DEPAKOTE, a twice-a-day or three times-a-day schedule may be instituted in selected patients.

The frequency of adverse effects (particularly elevated liver enzymes) may be dose related. The benefit of improved seizure control which may accompany higher doses should therefore be weighed against the possibility of a greater incidence of adverse reactions.

A good correlation has not been established between daily dose, serum level and therapeutic effect. However, therapeutic valproate serum levels for most patients will range from 50 to 100 mcg/ml. Occasional patients may be controlled with serum levels lower or higher than this range.

As the DEPAKOTE dosage is titrated upward, blood levels of phenobarbital and/or phenytoin may be affected. (See "Precautions" section.)

Patients who experience GI irritation may benefit from administration of the drug with food or by slowly building up the dose from an initial low level.

**HOW SUPPLIED**: DEPAKOTE (divalproex sodium enteric-coated tablets) are supplied as:

| | |
|---|---|
| 125 mg salmon pink colored tablets | |
| Bottles of 100 | (**NDC** 0074-6212-13) |
| 250 mg peach colored tablets | |
| Bottles of 100 | (**NDC** 0074-6214-13) |
| Abbo-Pac® unit dose packages of 100 | (**NDC** 0074-6214-11) |
| 500 mg lavender-colored tablets | |
| Bottles of 100 | (**NDC** 0074-6215-13) |
| Abbo-Pac® unit dose packages of 100 | (**NDC** 0074-6215-11) |


**REFERENCES**

1. Centers for Disease Control. Valproate: A New Cause of Birth Defects — Report from Italy and Follow-up from France. *Morbidity and Mortality Weekly Report* 32(33): 438-439, August 26, 1983.
2. Wilder, B.J., et al. Gastrointestinal Tolerance of Divalproex Sodium. *Neurology* 33: 808-811, June, 1983.
3. Wilder, B.J., et al. Twice-Daily Dosing of Valproate with Divalproex. *Clin Pharmacol Ther* 34(4): 501-504, 1983.


Revised Jan., 1986


**Abbott Health Care Products, Inc.**
**North Chicago, IL 60064**


7033813

**MD's: Don't Miss The Opportunity Of A Lifetime!**

PPS is now searching for 10 Family Practice and five Internal Medicine M.D.'s for a new practice in dramatically growing, upscale Rancho Cucamonga, just east of L.A.

Positions are available in April with additional placements in July for Pediatrics, OB-GYN and Orthopedic Surgery, plus additional FP and IM. Partnership, $6 – $7/K monthly guarantee plus fee-for-service; benefit package.

Don't miss this groundfloor opportunity. Call now to arrange a confidential interview with Ruthan Smith, Director of Physician Resources, (714) 825-4401.

P.S. Opportunities also available in Urgent Care, Emergency Medicine and most specialty fields. Other group practice opportunities in Greater San Bernardino-Riverside. Inquiries invited.

**PACIFIC PHYSICIAN SERVICES**

health care you can live with

12 North Fifth Street
Redlands, California 92373

# In Memoriam

## *California Medical Association*

ABBOTT, DEE L, Bakersfield. Died Jan 19, 1987, aged 89. Graduate of University of Nebraska, Omaha, 1927. Licensed in California in 1936. Dr Abbott was a member of the Kern County Medical Society.

BAKER, DONALD DUANE, San Francisco. Died Jan 12, 1987, aged 55. Graduate of University of California, San Francisco, 1956. Licensed in California in 1962. Dr Baker was a member of the San Francisco Medical Society.

BEAVER, MEREDITH G., Redlands. Died Jan 11, 1987, aged 87. Graduate of University of Oregon, Portland, 1926. Dr Beaver was a member of the San Bernardino County Medical Society.

BOBBITT, JAMES R. Died Oct 16, 1986, aged 74. Graduate of University of Southern California, 1943. Licensed in California in 1943. Dr Bobbitt was a member of the Los Angeles County Medical Association.

BUTLER, FRANCIS H., Whittier. Died Dec 11, 1986, aged 71. Graduate of University of Louisville School of Medicine, 1941. Licensed in California in 1942. Dr Butler was a member of the Los Angeles County Medical Association.

CARROLL, VINCENT P., Laguna Beach. Died Dec 2, 1986, aged 82. Graduate of University of California, Irvine. Dr Carroll was a member of the Orange County Medical Association.

CAVELTI, PHILIP A. Died Dec 29, 1986, aged 72. Graduate of University of Bern Medical School, Switzerland, 1939. Licensed in California in 1950. Dr Cavelti was a member of the Santa Clara County Medical Society.

FILLMORE, JOHN R., Strathmore. Died Dec 31, 1986, aged 83. Graduate of Northwestern University Medical School, Chicago, 1931. Licensed in California in 1931. Dr Fillmore was a member of the Tulare County Medical Society.

FOSTER, PAUL D. Died Jan 10, 1987, aged 82. Graduate of Loma Linda University, 1933. Licensed in California in 1933. Dr Foster was a member of the Los Angeles County Medical Association and a past president of the California Medical Association.

GIBSON, THOMAS E. Died Dec 26, 1986, aged 89. Graduate of University of California, San Francisco, 1922. Dr Gibson was a member of the San Francisco Medical Society.

HAMBLIN, MERRIMAN, Ontario. Died Jan 29, 1987, aged 71. Graduate of University of Tennessee College of Medicine, Memphis, 1938. Licensed in California in 1943. Dr Hamblin was a member of the San Bernardino County Medical Society.

HEPPNER, MYER J., Los Angeles. Died Oct 6, 1986, aged 86. Graduate of Stanford University, 1934. Licensed in California in 1934. Dr Heppner was a member of the Los Angeles County Medical Association.

JACKSON, B. RICHARD, Los Angeles. Died Dec 25, 1986, aged 68. Graduate of Temple University School of Medicine, Philadelphia, 1943. Licensed in California in 1954. Dr Jackson was a member of the Los Angeles County Medical Association.

JOHNSON, NEILL P., Stockton. Died Dec 10, 1986, aged 82. Graduate of Baylor Medical School, Houston, 1928. Licensed in California in 1928. Dr Johnson was a member of the San Joaquin County Medical Society.

JOHNSON, RUSSELL 1., Midway City. Died Oct 21, 1986, aged 86. Graduate of Loma Linda University, 1929. Licensed in California in 1929. Dr Johnson was a member of the Orange County Medical Association.

JONES, WILLIAM G. A., San Leandro. Died Dec 24, 1986, aged 68. Graduate of University of Colorado, 1942. Licensed in California in 1946. Dr Jones was a member of the Alameda-Contra Costa Medical Association.

KIMBALL, LLOYD O., Stockton. Died Jan 8, 1987, aged 61. Graduate of University of Utah, Salt Lake City, 1951. Licensed in California in 1951. Dr Kimball was a member of the San Joaquin County Medical Society.

KING, LOUISE S., Agnew. Died Dec 30, 1986, aged 91. Graduate of Columbia University, New York, 1923. Dr King was a member of the Santa Clara County Medical Society.

LEE, HENRY YEN. Died Oct 28, 1986, aged 75. Graduate of Loma Linda University, 1937. Licensed in California in 1937. Dr Lee was a member of the Los Angeles County Medical Association.

LONGLEY, JAMES E., Columbia. Died Dec 11, 1986, aged 75. Graduate of University of Tennessee, Memphis, 1937. Licensed in California in 1940. Dr Longley was a member of the San Joaquin County Medical Society.

MCLIN, EDWARD D., San Francisco. Died Dec 24, 1986, aged 71. Graduate of Stanford University, 1941. Licensed in California in 1941. Dr McLin was a member of the San Francisco Medical Society.

MCNAUGHT, ROBERT C. Died Dec 29, 1986, aged 80. Graduate of Stanford University, 1931. Dr McNaught was a member of the San Francisco Medical Society.

MCREYNOLDS, CHESTER C., Downey. Died Nov 26, 1986, aged 77. Graduate of Loma Linda University, 1936. Licensed in California in 1937. Dr McReynolds was a member of the Los Angeles County Medical Association.

MALIS, SOLOMON. Died Nov 22, 1986, aged 88. Graduate of University of Manitoba, Winnipeg, 1924. Dr Malis was a member of the San Diego County Medical Society.

*(Continued on Page 532)*

# Motrin® 800 mg TABLETS

ibuprofen

## a stronger reason to prescribe Motrin Tablets

©1986 The Upjohn Company

# Motrin® 800 TABLETS mg
ibuprofen

## Extra-Strength Motrin Tablets— a convenient way to tap the full potential of Motrin:

**The newest strength of *Motrin* Tablets**

**makes treatment easier** for arthritis patients who need the doses that provide higher levels of anti-inflammatory activity as well as potent analgesia...just 1 tablet t.i.d. provides 2400 mg/day.

**expands the dosage convenience** of MOTRIN Tablets – makes it even easier to adjust the dosage of MOTRIN to each patient's needs...the dosage range of up to 3200 mg/day can be achieved on a q.i.d. regimen. Gastroscopic studies at varying doses show an increased tendency toward gastric irritation at higher doses. However, at comparable doses, gastric irritation is about half that seen with aspirin.

**provides economy...**patients should pay less for MOTRIN Tablets than for comparable dosages of sulindac, piroxicam, or naproxen.

**provides, above all, the experience-proven efficacy and safety profile of *Motrin.*** MOTRIN continues to be America's most often prescribed nonsteroidal anti-inflammatory agent.

Please see adjacent page for a brief summary of prescribing information.

Upjohn 100 A Century of Caring 1886·1986

**MOTRIN® Tablets**
(ibuprofen)

**CONTRAINDICATIONS:** Anaphylactoid reactions have occurred in individuals hypersensitive to MOTRIN or with the syndrome of nasal polyps, angioedema and bronchospastic reactivity to aspirin or other nonsteroidal anti-inflammatory agents.

**WARNINGS:** Peptic ulceration and G.I. bleeding, sometimes severe, have been reported. Ulceration, perforation and bleeding may end fatally. An association has not been established. Use MOTRIN under close supervision in patients with a history of upper gastrointestinal tract disease, after consulting ADVERSE REACTIONS. In patients with active peptic ulcer and active rheumatoid arthritis, try nonulcerogenic drugs, such as gold. If MOTRIN is used, observe the patient closely for signs of ulcer perforation or G.I. bleeding.

**PRECAUTIONS:** Blurred and/or diminished vision, scotomata, and/or changes in color vision have been reported. If these develop, discontinue MOTRIN and the patient should have an ophthalmologic examination, including central visual fields and color vision testing.

Fluid retention and edema have been associated with MOTRIN; use with caution in patients with a history of cardiac decompensation or hypertension.

MOTRIN can inhibit platelet aggregation and prolong bleeding time. Use with caution in persons with intrinsic coagulation defects and on anticoagulant therapy.

Patients should report signs or symptoms of gastrointestinal ulceration or bleeding, blurred vision, skin rash, weight gain, or edema.

Patients on prolonged corticosteroid therapy should have therapy tapered slowly when MOTRIN is added.

The antipyretic, anti-inflammatory activity of MOTRIN may mask inflammation and fever.

As with other nonsteroidal anti-inflammatory drugs, borderline elevations of liver tests may occur in up to 15% of patients. These abnormalities may progress, may remain essentially unchanged, or may be transient with continued therapy. Meaningful elevations of SGPT or SGOT (AST) occurred in controlled clinical trials in less than 1% of patients. Severe hepatic reactions, including jaundice and cases of fatal hepatitis, have been reported with ibuprofen as with other nonsteroidal anti-inflammatory drugs. If liver disease develops or if systemic manifestations occur (e.g. eosinophilia, rash, etc.), MOTRIN should be discontinued.

In cross-study comparisons with 1200 mg to 3200 mg daily for several weeks, a slight dose-response decrease in hemoglobin/hematocrit was noted. The total decrease in hemoglobin usually does not exceed 1 gram.

**Renal Effects:** Long term administration of ibuprofen and other NSAIO's to animals has resulted in renal papillary necrosis and other abnormal renal pathology. In humans, there have been reports of acute interstitial nephritis with hematuria, proteinuria, and occasionally nephrotic syndrome. In patients with prerenal conditions and reduced renal blood flow or blood volume, NSAID's may precipitate overt renal decompensation. Patients with impaired renal function, heart failure, liver dysfunction, those taking diuretics and the elderly are at greatest risk. Discontinuation of NSAIO therapy is typically followed by recovery to the pretreatment state.

In patients with renal impairment, reduced dosage may be necessary. Prospective studies of MOTRIN safety in patients with chronic renal failure have not been done.

**Drug Interactions: Aspirin:** Used concomitantly may decrease MOTRIN blood levels.

**Coumarin:** Bleeding has been reported in patients taking MOTRIN and coumarin.

**Pregnancy and nursing mothers:** MOTRIN should not be taken during pregnancy or by nursing mothers.

**ADVERSE REACTIONS:** The most frequent type of adverse reaction occurring with MOTRIN is gastrointestinal of which one or more occurred in 4% to 16% of the patients. Reported side effects were higher at 3200 than at 2400 mg/day or less.

***Incidence Greater than 1% (but less than 3%) – Probable Causal Relationship***

**GASTROINTESTINAL:** Nausea,* epigastric pain,* heartburn,* diarrhea, abdominal distress, nausea and vomiting, indigestion, constipation, abdominal cramps or pain, fullness of GI tract (bloating and flatulence); **CENTRAL NERVOUS SYSTEM:** Oizziness,* headache, nervousness; **DERMATOLOGIC:** Rash* (including maculopapular type), pruritus; **SPECIAL SENSES:** Tinnitus; **METABOLIC/ENDOCRINE:** Decreased appetite; **CARDIOVASCULAR:** Edema, fluid retention (generally responds promptly to drug discontinuation; see PRECAUTIONS).

***Incidence less than 1% Probable Causal Relationship*****

**GASTROINTESTINAL:** Gastric or duodenal ulcer with bleeding and/or perforation, gastrointestinal hemorrhage, melena, gastritis, hepatitis, jaundice, abnormal liver function tests; **CENTRAL NERVOUS SYSTEM:** Oepression, insomnia, confusion, emotional lability, somnolence, aseptic meningitis with fever and coma; **OERMATOLOGIC:** Vesiculobullous eruptions, urticaria, erythema multiforme, Stevens-Johnson syndrome, alopecia; **SPECIAL SENSES:** Hearing loss, amblyopia (blurred and/or diminished vision, scotomata and/or changes in color vision) (see PRECAUTIONS); **HEMATOLOGIC:** Neutropenia, agranulocytosis, aplastic anemia, hemolytic anemia (sometimes Coombs positive), thrombocytopenia with or without purpura, eosinophilia, decreases in hemoglobin and hematocrit (see PRECAUTIONS); **CAROIOVASCULAR:** Congestive heart failure in patients with marginal cardiac function, elevated blood pressure, palpitations; **ALLERGIC:** Syndrome of abdominal pain, fever, chills, nausea and vomiting; anaphylaxis, bronchospasm (see CONTRAINDICATIONS); **RENAL:** Acute renal failure in patients with pre-existing significantly impaired renal function, decreased creatinine clearance, polyuria, azotemia, cystitis, hematuria; **MISCELLANEDUS:** Ory eyes and mouth, gingival ulcer, rhinitis.

***Incidence less than 1% – Causal Relationship Unknown*****

**GASTROINTESTINAL:** Pancreatitis; **CENTRAL NERVOUS SYSTEM:** Paresthesias, hallucinations, dream abnormalities, pseudotumor cerebri; **DERMATOLOGIC:** Toxic epidermal necrolysis, photoallergic skin reactions; **SPECIAL SENSES:** Conjunctivitis, diplopia, optic neuritis, cataracts; **HEMATOLOGIC:** Bleeding episodes (e.g. epistaxis, menorrhagia); **METABOLIC/ENOOCRINE:** Gynecomastia, hypoglycemic reaction, acidosis; **CARDIOVASCULAR:** Arrhythmias (sinus tachycardia, sinus bradycardia); **ALLERGIC:** Serum sickness, lupus erythematosus syndrome, Henoch-Schonlein vasculitis, angioedema; **RENAL:** Renal papillary necrosis.

*Reactions occurring in 3% to 9% of patients treated with MOTRIN. (Those reactions occurring in less than 3% of the patients are unmarked).

**Reactions are classified under **"Probable Causal Relationship (PCR)"** if there has been one positive rechallenge or if three or more cases occur which might be causally related. Reactions are classified under **"Causal Relationship Unknown"** if seven or more events have been reported but the criteria for PCR have not been met.

**OVERDOSAGE:** In cases of acute overdosage, the stomach should be emptied. The drug is acidic and excreted in the urine so alkaline diuresis may be beneficial.

**OOSAGE AND ADMINISTRATION:** Do not exceed 3200 mg/day.

Rheumatoid and osteoarthritis: Suggested dosage is 1200 to 3200 mg per day (400, 600 or 800 mg t.i.d. or q.i.d.). The smallest effective dosage should be used. Mild to moderate pain: 400 mg every 4 to 6 hours as necessary.

**HOW SUPPLIEO:**

| MOTRIN Tablets, 400 mg (orange) | MOTRIN Tablets, 600 mg (peach) | MOTRIN Tablets, 800 mg (apricot) |
|---|---|---|
| Bottles of 500 | Bottles of 500 | Bottles of 100 |
| Unit-dose package of 100 | Unit-dose package of 100 | Bottles of 500 |
| Unit of Use bottles of 100 | Unit of Use bottles of 100 | |

**CAUTION:** FEOERAL LAW PROHIBITS OISPENSING WITHOUT PRESCRIPTION.

**For additional product information, see your Upjohn representative or consult the package insert.**

MED B-9-S

Upjohn

A Century of Caring
1886·1986

February 1986
J-6321



# Books Received

*(Continued from Page 423)*

**INTERPRETING CARDIAC DYSRHYTHMIAS**—J. Marcus Wharton, MD, Fellow in Cardiology and Electrophysiology, Duke University School of Medicine, Durham, North Carolina, and Nora Goldschlager, MD, Clinical Professor of Medicine, University of California, San Francisco, School of Medicine, and Director, Coronary Care Unit and Electrocardiographic Laboratory, San Francisco General Hospital Medical Center. Medical Economics Books, Oradell, NJ 07649, 1987. 241 pages, price not given (paperback).

**KEY FACTS IN PATHOLOGY**—Para Chandrasoma, MD, MRCP(UK), Assistant Professor, Department of Pathology, University of Southern California School of Medicine, and Director of Surgical Pathology, Los Angeles County-USC Medical Center, and Clive R. Taylor, MD, DPhil, MRCPath, Professor and Chairman, Department of Pathology, University of Southern California School of Medicine, and Director of Laboratories and Pathology, Los Angeles County-USC Medical Center, Los Angeles. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1986. 417 pages, $27.50 (paperback).

**LABORATORY DIAGNOSIS IN OPHTHALMOLOGY**—Edited by Zeynel A. Karcioglu, MD, Professor of Ophthalmology and Pathology, Tulane University School of Medicine; Director, O'Brien Ocular Pathology Laboratory, Tulane Medical Center, and Director of Laboratories, Eye, Ear, Nose and Throat Hospital, New Orleans. Macmillan Publishing Co, 866 Third Ave, New York, NY 10022, 1987. 260 pages, $65 (cloth).

**LIVER PATHOLOGY—Volume 8 in Contemporary Issues in Surgical Pathology**—Edited by Robert L. Peters, MD, Professor of Pathology, USC School of Medicine, Los Angeles, and Chief Pathologist, USC Liver Unit, Rancho Los Amigos Medical Center, Downey, California, and John R. Craig, MD, PhD, Associate Clinical Professor of Pathology, USC School of Medicine, Los Angeles, and Chief Pathologist, St Luke Medical Center, Pasadena, California. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1986. 373 pages, $65.

**MAGNETIC RESONANCE IMAGING AND SPECTROSCOPY**—Edited by Fred A. Mettler, Jr, MD, MPH, Professor and Chairman, Department of Radiology, University of New Mexico Hospital, Albuquerque; Lawrence R. Muroff, MD, Clinical Professor of Radiology, University of South Florida College of Medicine, and Director, Division of Magnetic Resonance Imaging, Computed Tomography, and Nuclear Medicine, University Community Hospital, Tampa, and Madan V. Kulkarni, MD, Assistant Professor, Department of Radiology and Radiological Sciences, Vanderbilt University School of Medicine, and Clinical Director, Magnetic Resonance, Vanderbilt University Medical Center, Nashville, Tenn. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1986. 309 pages, $59.

**MANAGEMENT OF ADVANCED MELANOMA—Volume 6 in Contemporary Issues in Clinical Oncology**—Edited by Larry Nathanson, MD, Professor of Medicine, School of Medicine, State University of New York at Stony Brook, and Director, Oncology-Hematology Division, Winthrop University Hospital, Mineola, New York. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1986. 258 pages, $39.50.

**MANAGING CHRONIC DISEASE**—Edited by C. Stewart Rogers, MD, Associate Professor of Medicine, University of North Carolina School of Medicine, Chapel Hill, and Internal Medicine Teaching Program, The Moses H. Cone Memorial Hospital, Greensboro, North Carolina; Jack D. McCue, MD, Associate Professor of Medicine, Tufts University School of Medicine, Boston, and Vice-Chairman of Medicine and Chief of General Medicine and Geriatric Service, Baystate Medical Center, Springfield, Massachusetts, and Peter Gal, PharmD, Clinical Associate Professor, School of Pharmacy, University of North Carolina School of Medicine, Chapel Hill, and Director of Pharmacy Research and Education, Greensboro Area Health Education Center, The Moses H. Code Memorial Hospital, Greensboro, North Carolina. Medical Economics Books, Oradell, NJ 07649, 1987. 421 pages, price not given (paperback).

**MANUAL OF ANESTHESIA IN CANCER CARE**—William S. Howland, MD, Chairman, Department of Critical Care, Memorial Sloan-Kettering Cancer Center, and Professor of Anesthesiology, Cornell University Medical College, New York; Sharon Marie Rooney, MD, Clinical Chief, Department of Anesthesiology, Memorial Sloan-Kettering Cancer Center, and Associate Professor of Clinical Anesthesiology, Cornell University Medical College, New York, and Paul L. Goldiner, MD, Professor and Chairman, Department of Anesthesia, Albert Einstein College of Medicine of Yeshiva University, Bronx, New York. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1986. 312 pages, $27 (paperback).

**MANUAL OF COMMON OPHTHALMIC SURGICAL PROCEDURES**—Edited by Charles D. Phelps, MD, Professor and Head, Department of Ophthalmology, and Hansjoerg E.J.W. Kolder, MD, PhD, Professor and Director, Cataract Service, Department of Ophthalmology, College of Medicine, University of Iowa Hospitals, Iowa City. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1986. 183 pages, $39.50 (paperback).

**MODERN TECHNIQUES OF ION TRANSPORT—Volume 15 in Contemporary Issues in Nephrology**—Edited by Barry M. Brenner, MD, Samuel A. Levine Professor of Medicine, Harvard Medical School, and Director, Renal Division and Laboratory of Kidney and Electrolyte Physiology, Brigham and Women's Hospital, Boston, and Jay H. Stein, MD, Professor and Chairman, Department of Medicine, University of Texas Health Science Center at San Antonio. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1986. 325 pages, $53.

**OBSTETRICS—NORMAL AND PROBLEM PREGNANCIES**—Edited by Steven G. Gabbe, MD, Professor of Obstetrics and Gynecology and Pediatrics, University of Pennsylvania School of Medicine, and Director, Jerrold R. Golding Division of Fetal Medicine, Hospital of the University of Pennsylvania, Philadelphia; Jennifer R. Niebyl, MD, Associate Professor of Gynecology and Obstetrics and Pediatrics and Director, Division of Maternal-Fetal Medicine, The Johns Hopkins Medical Institutions, Baltimore, Maryland, and Joe Leigh Simpson, MD, Professor and Chairman, Department of Obstetrics and Gynecology, University of Tennessee, Memphis, College of Medicine. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1986. 1,092 pages, $75.

**OPEN-ANGLE GLAUCOMA—Volume 3 in Contemporary Issues in Ophthalmology**—Edited by George W. Weinstein, MD, Professor and Jane McDermott Shott Chairman, Department of Ophthalmology, West Virginia University Medical Center, Morgantown. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1986. 265 pages, $48.

# COMMITTED TO EXCELLENCE

ROCHE

PRESIDENT'S ACHIEVEMENT AWARD

## Presenting the winners of the 1987 Roche President's Achievement Awards

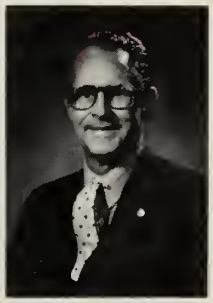
Hoffmann-La Roche is pleased to honor these outstanding sales representatives, chosen for their unparalleled dedication to the health-care field, professionalism and consistent high level of performance. Please join us in congratulating these exceptional individuals.

Kathryn Akin-Havrilla

David W. Anderson

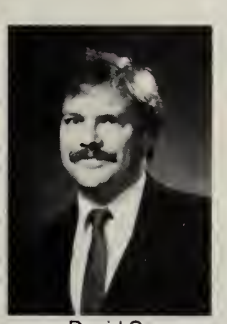
Steven W. Andre

Earl M. Butner



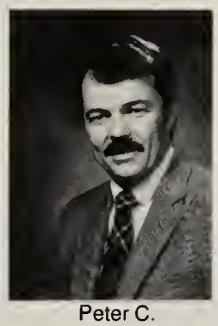
Dudley A. Desler

Robert J. Krause



David C. Lord

Thomas R. Lux



Peter C. McGregor

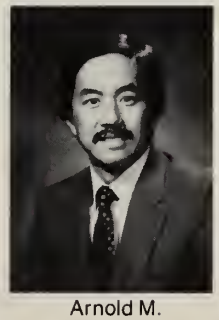
Antonio F. Ochoa

Roger V. Person

John D. Russell

Stanley J. Smithtro

Barbara K. Whitman



Arnold M. Yee

Bertram K. Yee

**Turn to the following page and find out how your award-winning Roche representative can help both you *and* your patients.**

# YOUR ROCHE REPRESENTATIVE WOULD LIKE YOU TO HAVE SOMETHING THAT WILL...

ROCHE®

**... improve patient satisfaction with office visits**

**... improve patient compliance with your instructions**

**... reduce follow-up calls to clarify instructions**

## The new Roche product books

- **Offer a supplement to, not a substitute for, patient contact**
- **Support your specific instructions to the patient**
- **Provide a long-term reinforcement of your oral counseling**

Because you are the primary source of medical information for your patients, we invite you to look over the Roche Product Booklets shown below and ask your Roche representative for a complimentary supply of those applicable to your practice.

ROCHE MEDICATION ME EDUCATION

Medicines that matter from people who care

# When considering professional liability protection, choose the Mutual Protection Trust

| Specialty | 1987 CAP/MPT Estimated Cost* |
|---|---|
| Allergy | $ 2,371 |
| Anesthesia | 15,840 |
| Cardiology with invasive vascular procedures | 10,924 |
| Cardiology — no invasive vascular procedures | 5,222 |
| Dermatology — no radiation or hair transplants | 5,222 |
| Gastroenterology with endoscopy and ERCP, board certified | 8,073 |
| Family Practice — no surgery | 5,222 |
| Family Practice — minor surgery or assisting at surgery | 8,073 |
| Family Practice — major surgery | 17,905 |
| General Surgery | 17,905 |
| Internal Medicine with invasive vascular procedures | 10,924 |
| Internal Medicine — no invasive vascular procedures | 5,222 |
| Neurology — no electro-convulsive therapy | 2,371 |
| Ophthalmology with surgery or laser | 8,073 |
| Orthopedics with spinal surgery | 22,035 |
| Orthopedics — no spinal surgery | 19,970 |
| Otolaryngology — doing plastic surgery, board certified | 17,905 |
| Pediatrics — General | 2,371 |
| Pediatrics — General, with invasive vascular procedures | 10,924 |
| Plastic Surgery, board certified | 17,905 |
| Psychiatry — no electro-convulsive therapy | 2,371 |
| Radiology — diagnostic, no coronary angiography | 5,222 |
| Radiology — including coronary angiography | 10,924 |
| Urology | 13,775 |

*These rates include dues and assessments for a CAP/MPT member with 50 or more months of membership or retroactive coverage (matured rate). CAP/MPT offers coverage limits of $1 million per occurrence with an aggregate of $3 million per year.

**CAP/MPT offers:**

- **EXPERIENCE: The oldest California Trust providing professional liability protection**
- QUALITY: Stringent screening process — each new member has a voice in the selection of new members
- **SAVINGS: Compare our cost with other experienced providers of malpractice protection**
- REINSURANCE: Limits assessment exposure
- **LOSS PREVENTION PROGRAMS: Education reduces malpractice risk**
- RETROACTIVE COVERAGE: For qualified members

In addition to dues and assessments, CAP/MPT members pay a one-time initial trust contribution based on risk classification. This can be paid in installments and is refundable under the terms of the MPT Agreement.

**MUTUAL PROTECTION TRUST**

**Cooperative of American Physicians, Inc.**

P.O. Box 76998
Los Angeles, CA 90076-0998

## (800) 252-7706

Call to find out what your cost would be with MPT

CONTINUING MEDICAL EDUCATION

(Continued from Page 510)

144: 144th Evacuation Hospital, PO Box 8000, Salt Lake City 84108. (801) 524-3924.

OSS: Ogden Surgical Society, PO Box 9311, Ogden 84409.

PCMC: Primary Children's Medical Center, 320 12th Ave, Salt Lake City 84103. (801) 363-1221.

PVH: Pioneer Valley Hospital, 3460 S 4155 West, West Valley City 84120. (801) 968-9061.

SMH: St Mark's Hospital, 1200 E 3900 South, Salt Lake City 84117. (801) 268-7111.

UOS: Utah Ophthalmological Society, 540 E 500 South, Salt Lake City 84102. (801) 355-7477.

USH: Utah State Hospital, PO Box 270, Provo 84603-0270. (801) 373-4400.

UUMC: University of Utah Medical Center, 50 N Medical Dr, Salt Lake City 84132. (801) 581-2258.

UVH: Utah Valley Hospital, 1034 N Fifth West, Provo 84601. (801) 373-7850.

VAMC: Veterans Administration Medical Center, 500 Foothill Dr, Salt Lake City 84148. (801) 582-1565.

VVMC: Valley View Medical Center, 595 S 75 East, Cedar City 84720. (801) 586-6587.

# WASHINGTON

This listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. To list Category 1 programs here please send information at least two months in advance to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 900, Seattle, WA 98121; or phone (206) 441-WSMA.

Brochures and registration forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

April 15—**Anorectal.** Seattle. Wed. Gould Auditorium, Northwest Hospital. Contact: (206) 364-0500, #1621.

April 15-16 —**Introduction to Industrial Hygiene.** Seattle. Wed-Thurs. NW Center for Occupational Health and Safety. Contact: U/W Dept of Environmental Health, SC-34, Seattle 98195. (206) 543-1069.

April 17—**Basic Monitoring Laboratory.** Seattle. Fri. NW Center for Occupational Health and Safety. Contact: U/W Dept of Environmental Health, SC-34, Seattle 98195. (206) 543-1069.

### COURSE SPONSORS AND CONTACT INFORMATION

CME HARBORVIEW—Contact: Gayle Splater, Cytology Continuing Education, Dept. of Pathology, Harborview Medical Center, 325 Ninth Avenue, Seattle, WA 98104. (206) 223-5953.

CME PIERCE COUNTY—Contact: Mrs Maxine Bailey, Executive Director, College of Medical Education, 705 South Ninth, No. 203, Tacoma, WA 98405. (206) 627-7137.

U/W (UNIVERSITY OF WASHINGTON)—Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

WSMA—Washington State Medical Association, Continuing Medical Education, 2033 Sixth Ave, Suite 900, Seattle, WA 98121. (206) 441-9762.

VMMC (VIRGINIA MASON MEDICAL CENTER)—Contact: Linda Orgel, Division of Continuing Medical Education, Virginia Mason Medical Center, PO Box 900, Seattle, WA 98111. (206) 223-6898.

April 24-25—**Benton-Franklin County Medical Society's 3rd Annual CME Seminar.** Richland. Fri-Sat. Holiday Inn. Contact: A. K. Sen, MD, (509) 783-4186.

April 25—**Mason Clinic Day.** Seattle. Sat. Virginia Mason Medical Center. Contact: VMMC.

April 30—**Soft Tissue Sarcomas.** Seattle. Thurs. Swedish Hospital Medical Center. Contact: Office of Medical Education, (206) 386-2265.

May 1—**Head and Neck Cancer.** Seattle. Fri. Swedish Hospital Medical Center. Contact: Office of Medical Education, (206) 386-2265.

May 1—**Topics in Pulmonary Medicine: Obstructive Airflow Disease Treatment.** Seattle. Fri. Virginia Mason Medical Center. Contact: VMMC.

May 8—**Current Issues in Asbestos Control.** Seattle. Fri. NW Center for Occupational Health and Safety. Contact: U/W Dept of Environmental Health, SC-34, Seattle 98195. (206) 543-1069.

May 13—**Neonatal.** Seattle. Wed. Gould Auditorium, Northwest Hospital. Contact: (206) 364-0500, #1621.

May 14-15—**Clinical Microbiology.** Seattle. Thurs-Fri. Contact: U/W.

May 20—**Management of Benign and Malignant Breast Disease.** Seattle. Wed. U/W Health Sciences. Contact: U/W.

May 27—**Dermatology.** Seattle. Wed. Gould Auditorium, Northwest Hospital. Contact: (206) 364-0500, #1621.

May 28-29—**Workers Compensation Update.** Seattle. Thurs-Fri. NW Center for Occupational Health and Safety. Contact U/W.

June 3—**Flexible Sigmoidoscopy III or IV.** Seattle. Wed. Gould Auditorium, Northwest Hospital. Contact: (206) 364-0500, #1621.

June 17-19—**Family Violence.** Seattle. Wed-Fri. Kane Hall, U/W. Contact: U/W.

June 25-26—**Infectious Diseases.** Seattle. Thurs-Fri. Holiday Inn Crowne Plaza. Contact: (206) 364-0500, #1621.

July 19-23—**Reducing Risks From Environmental Chemicals Through Biotechnology.** Seattle. Sun-Thurs. NW Center for Occupational Health and Safety. Contact: U/W.

July 24-26—**WSSA: Seafair IX Regional Anesthesia.** Seattle. Fri-Sun. Virginia Mason Medical Center. Contact: VMMC.

July 27-31—**The Pathology of Lung Cancer.** Seattle. Mon-Fri. Virginia Mason Medical Center. Contact: VMMC.

# WYOMING

June 25-29—**Wyoming Medical Society Annual Meeting.** Jackson Lake Lodge, Moran. Thurs-Mon. Contact: WMS, PO Drawer 4009, Cheyenne 82003-4009. (307) 635-2424.

June 28-July 2—**Update on General Pediatrics.** University of Nebraska College of Medicine at Jackson Hole Racquet Club, Jackson. Sun-Thurs. Contact: Brenda Ram, Center for Continuing Education, Univ of Nebraska Medical Center, 42nd and Dewey Ave, Omaha, NE 68105. (402) 559-4152.

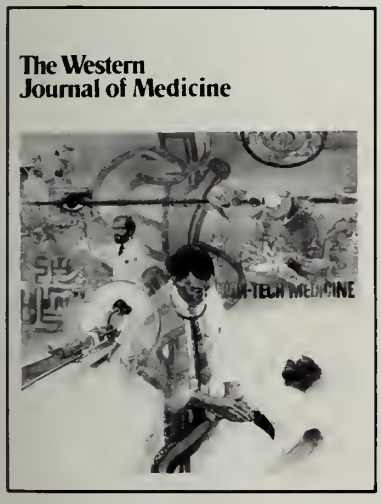
July 5-9—**Sports Medicine Update 1987.** University of Nebraska College of Medicine at Jackson Hole Racquet Club, Jackson. Sun-Thurs. Contact: Brenda Ram, Center for Continuing Education, Univ of Nebraska Medical Center, 42nd and Dewey Ave, Omaha, NE 68105. (402) 559-4152. ◆

# Medical Informatics

I would suggest that the computer in its relation to medicine is analogous to that of the microscope in the last century. . . . The analogous role that I believe the computer is now taking on is also that of a breakthrough tool—one enabling us to explore and better understand the informational and cognitive foundations of medicine. Its application to the classification and retrieval of data and to the management of information will result in a deeper insight into the structure of medical information and knowledge itself.

*—Marsden S. Blois, PhD, MD*

# High-Tech Medicine




Progress in medical science seems to come in rushes. There are long periods of time during which we mainly fine-tune the status quo: third-generation drugs, better optics for endoscopes, more accurate assays, rapid development of x-ray film and so forth. Then, out of nowhere, a surge of new discoveries whose potential applications to medical practice seem limitless takes our breath away. We are now in such an epoch. Powerful and precise lasers. Almost unbelievable organ transplantation. Complex and uniquely informative magnetic resonance imaging and positron emission tomography. Exquisitely specific monoclonal antibodies. And the immense potential of modern molecular biology. This rush of new advances, collapsed into such a brief period of time, boggles the mind.

*—R. Paul Robertson, MD*

SPECIAL ISSUES

| Quantity | Per Copy* |
|---|---|
| Single copy | $4.50 |
| 2 to 10 | 4.00 |
| 11 to 50 | 3.50 |
| More than 50 | 3.00 |

**Please send me:**

___ copies of Medical Informatics

___ copies of High-Tech Medicine

*Note: Domestic postage and handling included. Please add California & local sales tax where applicable. Foreign postage additional.

## ORDER FORM

Name _____

Address _____

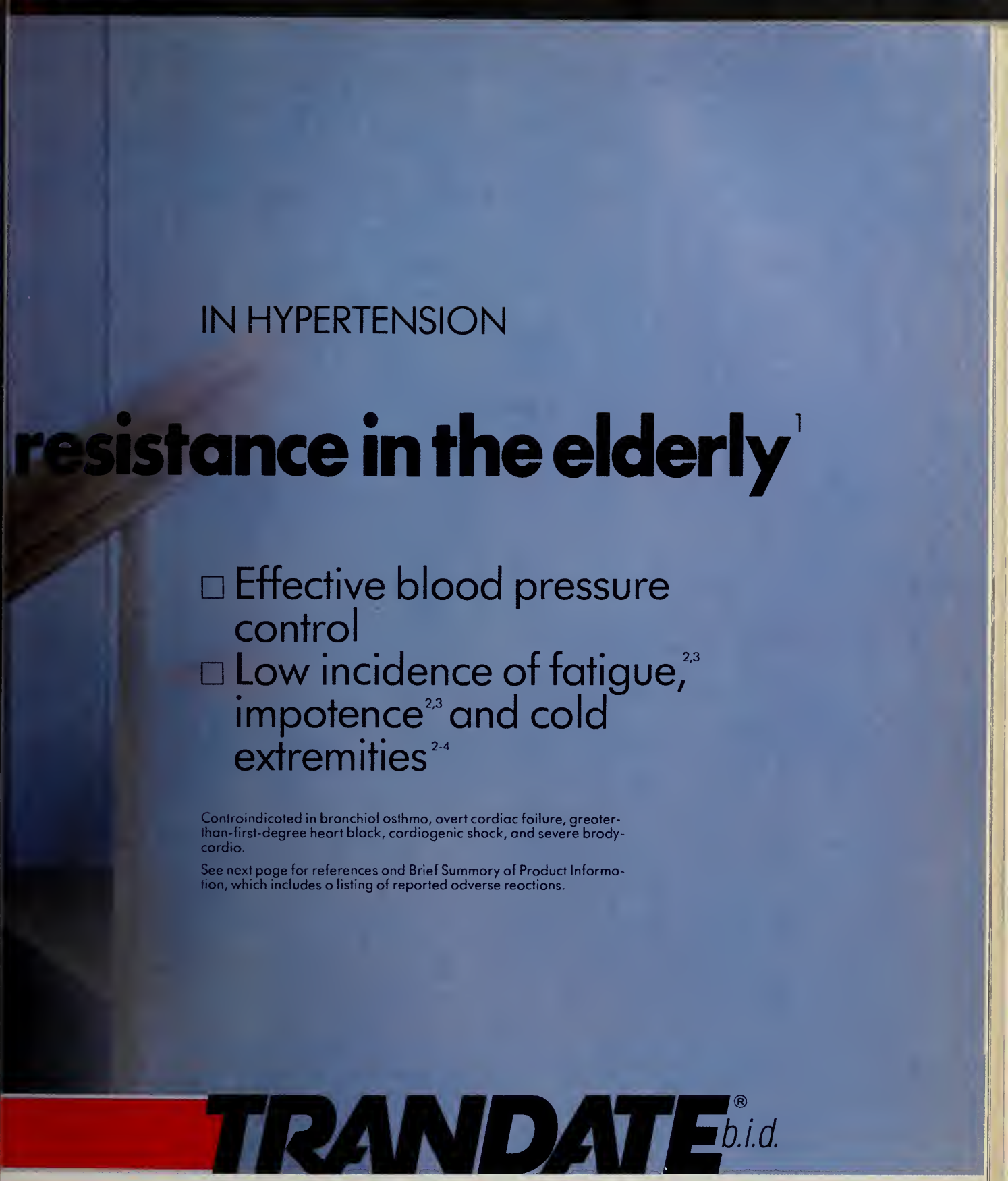
City/State/Zip _____

Total amount enclosed $_____

**Payment must accompany order.**

**Mail to:** Circulation Department, The Western Journal of Medicine
P.O. Box 7602, San Francisco, CA 94120-7602

Glaxo


IN HYPERTENSION
resistance in the elderly[1]
□ Effective blood pressure control
□ Low incidence of fatigue,[2,3] impotence[2,3] and cold extremities[2-4]
Contraindicated in bronchial asthma, overt cardiac failure, greater-than-first-degree heart block, cardiogenic shock, and severe bradycardia.
See next page for references and Brief Summary of Product Information, which includes a listing of reported adverse reactions.
TRANDATE® b.i.d.
labetalol HCl/Glaxo 100 mg/200 mg tablets
Because it also vasodilates

**References**: 1. Holtzman JL, Finley D, Johnson B, et al: The effects of single-dose atenolol, labetalol, and propranolol on cardiac and vascular function. *Clin Pharmacol Ther* 1986;40:268-273. 2. Due DL, Giguere GC, Plachetka JR. Postmarketing comparison of labetalol and propranolol in hypertensive patients. *Clin Ther* 1986;8(6):624-631. 3. Burris JF, Goldstein J, Zager PG, et al. Comparative tolerability of labetalol versus propranolol, atenolol, pindolol, metoprolol, and nadolol. *J Clin Hypertens* 1986;3:1-9 4. Erb RJ, Plachetka JR. Thermographic evaluation of the peripheral vascular effects of labetalol and propranolol. *Curr Ther Res* 1985;28(1):68-73.

**TRANDATE® Tablets**
**(labetalol hydrochloride)**

**BRIEF SUMMARY OF PRODUCT INFORMATION**

The following is a brief summary only. Before prescribing, see complete prescribing information in TRANDATE® Tablets product labeling.

**INDICATIONS AND USAGE:** TRANDATE® Tablets are indicated in the management of hypertension. TRANDATE Tablets may be used alone or in combination with other antihypertensive agents, especially thiazide and loop diuretics.

**CONTRAINDICATIONS:** TRANDATE® Tablets are contraindicated in bronchial asthma, overt cardiac failure, greater-than-first-degree heart block, cardiogenic shock, and severe bradycardia (see **WARNINGS**).

**WARNINGS: Cardiac Failure:** Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure. Beta-blockade carries a potential hazard of further depressing myocardial contractility and precipitating more severe failure. Although beta-blockers should be avoided in overt congestive heart failure, if necessary labetalol HCl can be used with caution in patients with a history of heart failure who are well compensated. Congestive heart failure has been observed in patients receiving labetalol HCl. Labetalol HCl does not abolish the inotropic action of digitalis on heart muscle.

**In Patients Without a History of Cardiac Failure:** In patients with latent cardiac insufficiency, continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or be given a diuretic, and the response should be observed closely. If cardiac failure continues despite adequate digitalization and diuretic, TRANDATE® therapy should be withdrawn (gradually, if possible).

**Exacerbation of Ischemic Heart Disease Following Abrupt Withdrawal:** Angina pectoris has not been reported upon labetalol HCl discontinuation. However, hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred after *abrupt* discontinuation of such therapy. When discontinuing chronically administered TRANDATE, particularly in patients with ischemic heart disease, the dosage should be gradually reduced over a period of one to two weeks and the patient should be carefully monitored. If angina markedly worsens or acute coronary insufficiency develops, TRANDATE administration should be reinstituted promptly, at least temporarily, and other measures appropriate for the management of unstable angina should be taken. Patients should be warned against interruption or discontinuation of therapy without the physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue TRANDATE therapy abruptly even in patients treated only for hypertension.

**Nonallergic Bronchospasm (eg, Chronic Bronchitis and Emphysema): Patients with bronchospastic disease should, in general, not receive beta-blockers.** TRANDATE may be used with caution, however, in patients who do not respond to, or cannot tolerate, other antihypertensive agents. It is prudent, if TRANDATE is used, to use the smallest effective dose, so that inhibition of endogenous or exogenous beta-agonists is minimized.

**Pheochromocytoma:** Labetalol HCl has been shown to be effective in lowering blood pressure and relieving symptoms in patients with pheochromocytoma. However, paradoxical hypertensive responses have been reported in a few patients with this tumor; therefore, use caution when administering labetalol HCl to patients with pheochromocytoma.

**Diabetes Mellitus and Hypoglycemia:** Beta-adrenergic blockade may prevent the appearance of premonitory signs and symptoms (eg, tachycardia) of acute hypoglycemia. This is especially important with labile diabetics. Beta-blockade also reduces the release of insulin in response to hyperglycemia; it may therefore be necessary to adjust the dose of antidiabetic drugs.

**Major Surgery:** The necessity or desirability of withdrawing beta-blocking therapy prior to major surgery is controversial. Protracted severe hypotension and difficulty in restarting or maintaining a heartbeat have been reported with beta-blockers. The effect of labetalol HCl's alpha-adrenergic activity has not been evaluated in this setting.

A synergism between labetalol HCl and halothane anesthesia has been shown (see **Drug Interactions** under **PRECAUTIONS**).

**PRECAUTIONS: General:** ***Impaired Hepatic Function:*** TRANDATE® Tablets should be used with caution in patients with impaired hepatic function since metabolism of the drug may be diminished.

***Jaundice or Hepatic Dysfunction:*** On rare occasions, labetalol HCl has been associated with jaundice (both hepatic and cholestatic). It is therefore recommended that treatment with labetalol HCl be stopped immediately should a patient develop jaundice or laboratory evidence of liver injury. Both have been shown to be reversible on stopping therapy.

**Information for Patients:** As with all drugs with beta-blocking activity, certain advice to patients being treated with labetalol HCl is warranted. This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects. While no incidence of the abrupt withdrawal phenomenon (exacerbation of angina pectoris) has been reported with labetalol HCl, dosing with TRANDATE Tablets should not be interrupted or discontinued without a physician's advice. Patients being treated with TRANDATE Tablets should consult a physician at any sign of impending cardiac failure. Also, transient scalp tingling may occur, usually when treatment with TRANDATE Tablets is initiated (see **ADVERSE REACTIONS**).

**Laboratory Tests:** As with any new drug given over prolonged periods, laboratory parameters should be observed over regular intervals. In patients with concomitant illnesses, such as impaired renal function, appropriate tests should be done to monitor these conditions.

**Drug Interactions:** In one survey, 2.3% of patients taking labetalol HCl in combination with tricyclic antidepressants experienced tremor as compared to 0.7% reported to occur with labetalol HCl alone. The contribution of each of the treatments to this adverse reaction is unknown, but the possibility of a drug interaction cannot be excluded.

Drugs possessing beta-blocking properties can blunt the bronchodilator effect of beta-receptor agonist drugs in patients with bronchospasm; therefore, doses greater than the normal antiasthmatic dose of beta-agonist bronchodilator drugs may be required.

Cimetidine has been shown to increase the bioavailability of labetalol HCl. Since this could be explained either by enhanced absorption or by an alteration of hepatic metabolism of labetalol HCl, special care should be used in establishing the dose required for blood pressure control in such patients.

Synergism has been shown between halothane anesthesia and intravenously administered labetalol HCl. During controlled hypotensive anesthesia using labetalol HCl in association with halothane, high concentrations (3% or above) of halothane should not be used because the degree of hypotension will be increased and because of the possibility of a large reduction in cardiac output and an increase in central venous pressure. The anesthesiologist should be informed when a patient is receiving labetalol HCl.

Labetalol HCl blunts the reflex tachycardia produced by nitroglycerin without preventing its hypotensive effect. If labetalol HCl is used with nitroglycerin in patients with angina pectoris, additional antihypertensive effects may occur.

**Drug/Laboratory Test Interactions:** The presence of a metabolite of labetalol in the urine may result in falsely increased levels of urinary catecholamines when measured by a nonspecific trihydroxyindole (THI) reaction. In screening patients suspected of having a pheochromocytoma and being treated with labetalol HCl, specific radioenzymatic or high performance liquid chromatography assay techniques should be used to determine levels of catecholamines or their metabolites.

**Carcinogenesis, Mutagenesis, Impairment of Fertility:** Long-term oral dosing studies with labetalol HCl for 18 months in mice and for two years in rats showed no evidence of carcinogenesis. Studies with labetalol HCl using dominant lethal assays in rats and mice and exposing microorganisms according to modified Ames tests showed no evidence of mutagenesis.

**Pregnancy:** ***Teratogenic Effects: Pregnancy Category C:*** Teratogenic studies have been performed with

**TRANDATE® Tablets (labetalol hydrochloride)**

labetalol in rats and rabbits at oral doses up to approximately six and four times the maximum recommended human dose (MRHD), respectively. No reproducible evidence of fetal malformations was observed. Increased fetal resorptions were seen in both species at doses approximating the MRHD. There are no adequate and well-controlled studies in pregnant women. Labetalol should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

***Nonteratogenic Effects:*** Infants of mothers who were treated with labetalol HCl during pregnancy did not appear to be adversely affected by the drug. Oral administration of labetalol to rats during late gestation through weaning at doses of two to four times the MRHD caused a decrease in neonatal survival.

**Labor and Delivery:** Labetalol HCl given to pregnant women with hypertension did not appear to affect the usual course of labor and delivery.

**Nursing Mothers:** Small amounts of labetalol (approximately 0.004% of the maternal dose) are excreted in human milk. Caution should be exercised when TRANDATE Tablets are administered to a nursing woman.

**Pediatric Use:** Safety and effectiveness in children have not been established.

**ADVERSE REACTIONS:** Most adverse effects are mild, transient, and occur early in the course of treatment. In controlled clinical trials of three to four months' duration, discontinuation of TRANDATE® Tablets due to one or more adverse effects was required in 7% of all patients. In these same trials, beta-blocker control agents led to discontinuation in 8% to 10% of patients, and a centrally acting alpha-agonist in 30% of patients.

The following adverse reactions were derived from multi-center, controlled clinical trials over treatment periods of three and four months. The rates, which ranged from less than 1% to 5% except as otherwise noted, are based on adverse reactions considered probably drug-related by the investigator. If all reports are considered, the rates are somewhat higher (eg, dizziness, 20%; nausea, 14%; fatigue, 11%).

***Body as a Whole:*** Fatigue, asthenia, and headache.

***Gastrointestinal:*** Nausea (6%), vomiting, dyspepsia, diarrhea, and taste distortion.

***Central and Peripheral Nervous Systems:*** Dizziness (11%), paresthesia, and drowsiness.

***Autonomic Nervous System:*** Nasal stuffiness, ejaculation failure, impotence, and increased sweating.

***Cardiovascular:*** Edema and postural hypotension.

***Respiratory:*** Dyspnea.

***Skin:*** Rash.

***Special Senses:*** Vision abnormality and vertigo.

The adverse effects were reported spontaneously and are representative of the incidence of adverse effects that may be observed in a properly selected hypertensive patient population, ie, a group excluding patients with bronchospastic disease, overt congestive heart failure, or other contraindications to beta-blocker therapy.

Clinical trials also included studies utilizing daily doses up to 2,400 mg in more severely hypertensive patients. The US therapeutic trials data base for adverse reactions that are clearly or possibly dose-related shows that the following side effects increased with increasing dose: dizziness, fatigue, nausea, vomiting, dyspepsia, paresthesia, nasal stuffiness, ejaculation failure, impotence, and edema.

In addition, a number of other less common adverse events have been reported in clinical trials or the literature:

***Cardiovascular:*** Postural hypotension, including rarely, syncope.

***Central and Peripheral Nervous Systems:*** Paresthesias, most frequently described as scalp tingling. In most cases, it was mild, transient, and usually occurred at the beginning of treatment.

***Collagen Disorders:*** Systemic lupus erythematosus; positive antinuclear factor (ANF).

***Eyes:*** Dry eyes.

***Immunological System:*** Antimitochondrial antibodies.

***Liver and Biliary System:*** Cholestasis with or without jaundice.

***Musculoskeletal System:*** Muscle cramps; toxic myopathy.

***Respiratory System:*** Bronchospasm.

***Skin and Appendages:*** Rashes of various types, such as generalized maculopapular, lichenoid, urticarial, bullous lichen planus, psoriaform, and facial erythema; Peyronie's disease; reversible alopecia.

***Urinary System:*** Difficulty in micturition, including acute urinary bladder retention.

Following approval for marketing in the United Kingdom, a monitored release survey involving approximately 6,800 patients was conducted for further safety and efficacy evaluation of this product. Results of this survey indicate that the type, severity, and incidence of adverse effects were comparable to those cited above.

**Potential Adverse Effects:** In addition, other adverse effects not listed above have been reported with other beta-adrenergic blocking agents.

***Central Nervous System:*** Reversible mental depression progressing to catatonia, an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance or neuropsychometrics.

***Cardiovascular:*** Intensification of AV block (see **CONTRAINDICATIONS**).

***Allergic:*** Fever combined with aching and sore throat; laryngospasm; respiratory distress.

***Hematologic:*** Agranulocytosis; thrombocytopenic or nonthrombocytopenic purpura.

***Gastrointestinal:*** Mesenteric artery thrombosis; ischemic colitis.

The oculomucocutaneous syndrome associated with the beta-blocker practolol has not been reported with labetalol HCl.

**Clinical Laboratory Tests:** There have been reversible increases of serum transaminases in 4% of patients treated with labetalol HCl and tested, and more rarely, reversible increases in blood urea.

**OVERDOSAGE:** Information concerning possible overdosage and its treatment appears in the full prescribing information.

**DOSAGE AND ADMINISTRATION:** DOSAGE MUST BE INDIVIDUALIZED. The recommended *initial* dosage is 100 mg *twice* daily whether used alone or added to a diuretic regimen. After two or three days, using standing blood pressure as an indicator, dosage may be titrated in increments of 100 mg bid every two or three days. The usual *maintenance* dosage of labetalol HCl is between 200 and 400 mg *twice* daily. Before use, see complete prescribing information for dosage details.

**HOW SUPPLIED:** TRANDATE® Tablets, 100 mg, light orange, round, scored, film-coated tablets engraved on one side with "TRANDATE 100 GLAXO," bottles of 100 (NDC 0173-0346-43) and 500 (NDC 0173-0346-44) and unit dose packs of 100 tablets (NDC 0173-0346-47).

TRANDATE Tablets, 200 mg, white, round, scored, film-coated tablets engraved on one side with "TRANDATE 200 GLAXO," bottles of 100 (NDC 0173-0347-43) and 500 (NDC 0173-0347-44) and unit dose packs of 100 tablets (NDC 0173-0347-47).

TRANDATE Tablets, 300 mg, peach, round, scored, film-coated tablets engraved on one side with "TRANDATE 300 GLAXO," bottles of 100 (NDC 0173-0348-43) and 500 (NDC 0173-0348-44) and unit dose packs of 100 tablets (NDC 0173-0348-47).

**TRANDATE Tablets should be stored between 2° and 30°C (36° and 86°F). TRANDATE Tablets in the unit dose boxes should be protected from excessive moisture.**

©Copyright 1984, Glaxo Inc. All rights reserved.

September 1986

Glaxo Inc.
Research Triangle Park, NC 27709

©1987, Glaxo Inc. TRN263 April 1987

# Classified Advertisements

The rate for each insertion is **$6 per line** (average six words per line) **with five line ($30) minimum.** Box number charge: $5 each month.

**Classified display rates $50 per inch.**

Copy for classified advertisements should be received not later than **25th of the second month preceding issue. All copy must be typed or printed.** • Classified advertisers using Box Numbers forbid the disclosure of their identity; your inquiries in writing will be forwarded to Box Number advertisers. The right is reserved to reject or modify all classified advertising copy in conformity with the decisions of the Advertising Committee.

**Please Type or Print Advertising Copy**

## Classified Advertisements Are Payable in Advance

CLASSIFIED ADVERTISEMENTS
THE WESTERN JOURNAL OF MEDICINE
P.O. BOX 7602, SAN FRANCISCO, CA 94120-7602

### PHYSICIANS WANTED

**ARIZONA BASED PHYSICIAN RECRUITMENT** firm has opportunities Coast to Coast. "Professionals working with Professionals." Over 14 years experience. Call (602) 990-8080; or send CV to: Mitchell & Associates, Inc., PO Box 1804, Scottsdale, AZ 85252.

**FAMILY PRACTICE PHYSICIAN**—provide primary care in clinics in rural New Mexico; some hospital; ER service; Obstetrics a must. Locations in Cuba, New Mexico, near the Jemez Mountains with skiing and mountain sports nearby. Board certified or Board eligible family practice desired. Excellent benefits. Please call Pat Sanchez, Personnel Director, Presbyterian Medical Services, PO Box 2267, Santa Fe, NM 87504; (505) 982-5565.

**INTERNIST/FAMILY PRACTICE—SAN FRANCISCO.** Rapidly growing practice needs BC/BE with California license. Opportunity for some subspecialty work in ENT, Ophthalmology, OB/GYN, Urology, Orthopedics. Large patient base, fully equipped lab, x-ray, pharmacy. Cantonese speaking preferred. Excellent salary/benefits package plus malpractice coverage and incentives. Assistance with relocation expenses. Send CV to Linda Yu Bien, Assistant Director, North East Medical Services, 1520 Stockton St., San Francisco, CA 94133.

**CALIFORNIA, SAN FRANCISCO BAY AREA:** Full-time career Emergency Physician wanted for high volume Emergency Department. Emergency Medicine Board certified or Board-ready mandatory to participate in a group of twenty full-time staff physicians seeing over 300 patients per day. Salaried position, excellent benefits include three weeks paid vacation; one week CME, paid malpractice, health and life insurance; corporate shareholdership in three years. Send CV or contact David Gallagher, MD, 27400 Hesperian Blvd., Hayward, CA 94545.

**ARIZONA EMERGENCY MEDICINE:** An emergency department Medical Directorship and staff positions are immediately available at two client hospitals located in Kingman and Lake Havasu City. Moderate volume emergency departments. Excellent nursing and medical staff support. We offer a guaranteed competitive rate of compensation, occurrence malpractice insurance coverage, CME allowance, reimbursement of professional dues. Directors also receive paid health benefits which include dependents. For additional information contact Bill Salmo, Spectrum Emergency Care, 6275 Lehman Dr., Ste C-202, Colorado Springs, CO 80918; 1 (800) 525-3681; (303) 590-1755.

### PHYSICIANS WANTED

**EDMONDS, WASHINGTON:** Scenic waterfront community 20 minutes north of Seattle. Physician owned clinic combined OB/GYN and Family Practice seeks additional OB/GYN for full- or part-time. We presently have 4 Family Practitioners and 2 OB/GYNs. Send CV to Philip DuBois, MD, 7935 216th St. S.W., Suite E, Edmonds, WA 98020; (206) 775-0681.

**FAMILY PRACTITIONER, INTERNIST OR EMERGENCY PHYSICIAN** sought for primary care clinic in 85-member multispecialty group. Expanded physical facility under construction. Low level trauma. Emphasis on internal medicine, cardiopulmonary, orthopedics and pediatrics. Short associate status leading to full membership. Incentive oriented compensation. Within 1½ to 2½ hours of Carmel, San Francisco, Yosemite and Lake Tahoe. Reply with CV and references to C. R. Maino, MD, Medical Director, Gould Medical Foundation, 600 Coffee Road, Modesto, CA 95355.

**OREGON.** Primary care position with community based clinic serving low income population. Outpatient/inpatient care with flexible scheduling and time off. Contact: Whitebird Clinic, 509 E. 13th, Eugene, OR 97401; (503) 484-4800.

**SAN DIEGO, CALIFORNIA**—Live and work in America's finest city. Career opportunities for full-time Family Practitioners and Internists. Expanding network of ambulatory care centers. Send CV in confidence to Mercy CarePoint Medical Group, 681 Encinitas Blvd., #406-P, Encinitas, CA 92024.

**FULL-TIME BOARD CERTIFIED FAMILY PRACTITIONER** sought by 8-physician department of Family Practice in 70-physician multispecialty group. No obstetrics. Full medical services available. Woodland is near Sacramento, 1½ hours from San Francisco and 2 hours from Lake Tahoe. Send CV to Michael Pirruccello, MD, 1207 Fairchild Court, Woodland, CA 95695; (916) 666-2466.

**CALIFORNIA:** An excellent opportunity is currently available to join team of physicians providing emergency department coverage at full service community hospital. Located in beautiful Redwood area of northern California. Guaranteed competitive rate of compensation, occurrence malpractice insurance coverage, allowance for CME, reimbursement of professional dues. For additional information on this opportunity contact Bill Salmo, Spectrum Emergency Care, 6275 Lehman Dr., Ste. C-202, Colorado Springs, CO 80918; 1 (800) 525-3681; (303) 590-1755.

**LAKE CHELAN, WA:** Looking for Family Practitioner to join two Board certified Family Physicians in a busy rural vacation paradise. Obstetrics required. Salary first year, with opportunity to establish your own private practice. Modern local hospital with 30 beds and close to a Regional Medical Center for patient referral. Lake Chelan is the Gateway to Stehekin and the North Cascade National Park. Position available immediately. Write to Lake Chelan Clinic, PO Box 368, Chelan, WA 98816 or call (509) 682-2511.

**BC/BE GENERAL INTERNIST** with or without subspecialty, to associate with five man internal medicine group in small northern California city. Modern, complete and expanding hospital. Generous salary plus percentage. Early partnership. Reply to Number 11, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602

**MONTEREY PENINSULA,** California Board certified/eligible general Internist to join five other Internists now in multispecialty group. Guaranteed income arrangement leading to partnership. Busy, well established clinic practice. Excellent office, lab, x-ray equipment. Outstanding community hospital. Submit CV, availability date to John D. Lord, MD, Central Medical Group, Monterey Peninsula, Pacific Grove, CA 93950.

**OREGON COAST:** Wanted BC/BE Family Practice physician to join 5 FPs in multispecialty group. OB included. Contact Kent Sharman, MD, at North Bend Medical Center, Inc., 1900 Woodland Dr., Coos Bay, OR 97420 or call (503) 267-5151 or (within Oregon) (800) 452-5863.

**FAMILY PRACTICE**—Northern San Francisco Bay area. Excellent opportunity for 2 BC/BE Family Practitioners to join growing dept. Full hospital privileges except OB. Prepaid HMO provides competitive salary and excellent benefits. Call or write Chief, Dept. of Family Practice, Kaiser Permanente Medical Center, 1550 Gateway Blvd., Fairfield, CA 94533; phone (707) 427-4200.

**NEUROLOGIST—B/C B/E** needed for growing practice in San Francisco Bay Area; consider joining this neurology medical group active in clinical neurology, with special emphasis on med-legal evaluations, occupational neurology and electrophysiology; prior experience in evaluations and an active interest in EMG/EEG/EP will be an asset. Please provide current CV, a letter outlining your professional goals, date available and an indication of your earning expectations. Respond to Box 164, 1550 California St., Ste. 6, San Francisco, CA 94109.

**ORTHOPEDIC SURGEON.** F/T Orthopedic Surgeon to join growing multispecialty group in southern California. Salary plus malpractice and benefits. Great potential for right physician; individual ownership. Send CV to Number 18, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

**DIRECTOR, FAMILY PRACTICE RESIDENCY IN BOISE, IDAHO,** 18 resident program affiliated with University of Washington. Board certification, teaching experience, private practice and administrative skills required. Academic appointment, salary and benefit package commensurate with experience. Application deadline April 15, 1987. Contact John Mohr, MD, Director, Family Practice Residency of Idaho, 777 N. Raymond, Boise, ID 83704.

**PHYSICIANS WANTED.** Physicians, BC/BE needed immediately to join expanding multispecialty group. Practice in rapidly growing Southwest community (population 500,000+). Fee-for-service and prepaid health care. Group includes Family Practice/Pediatrics, Internal Medicine/Subspecialties/24 hour Urgent Care. Teaching appointment. Position offers excellent compensation and benefits plus full pension and profit sharing. Relocation expenses. Interested individuals should reply with curriculum vitae to: Southwest Medical Associates, 333 N. Rancho Dr., Ste. 100, Las Vegas, NV 89106.

## SOUTHERN CALIFORNIA

Enjoy professional challenge and growth with a successful and expanding HMO in Southern California. CIGNA Healthplans of California is seeking Specialists and Primary Care physicians committed to concepts of prevention and health maintenance to join our facilities in Los Angeles and Orange Counties. We offer an excellent compensation and benefits package including profit sharing. For consideration, please forward CV to:

**Director/Physician Recruitment**
**CIGNA Healthplans of California**
**505 N. Brand Blvd., Suite 400-49**
**Glendale, CA 91203**

**SAN DIEGO, CALIFORNIA.** Exciting ground floor opportunities for physicians in primary care/ambulatory GYN (no OB) in provision of health care exclusively to women. Quality feminine surroundings. Salary plus incentive and malpractice coverage. Send CV to Centers for Women's Medicine Medical Group, 701 "B" Street, Ste. 330-WJM, San Diego, CA 92101.

**VICE PRESIDENT MEDICAL SERVICES.** Offers challenging opportunity to systems oriented physician for Prepaid Health Plan and fee for service medical center(s). Excellent salary and fringe benefits. Requires California Medical License; one year of formal training in health administration or two years experience in medical care management and proficiency in primary clinical care. Please submit Curriculum Vitae to James M. Clayton, CEO, FHFA, PO Box 30051, San Jose, CA 95156-9985. EOE.

**OREGON**—General Internist sought for busy practice. Multispecialty group of 10 physicians, 38 miles from Portland. CV to Administrator, Physicians' Medical Center, P.C., 420 East Fifth St., McMinnville, OR; Phone (503) 438-9551.

**ADDITIONAL INTERNIST NEEDED** for busy 5 physician multispecialty group. Beautiful, well-equipped 6 year old office just 75 feet from 34-bed hospital with ICU/CCU unit. This all Board certified group houses 3 Family Practitioners, 2 General Surgeons, and 1 Internist. Coastal retirement town offers top notch school system and excellent array of activities. Located just 75 easy miles from Portland adds even more cultural and shopping opportunities. For further information contact Rick Bigger days at North Coast Medical Center, P.C., Seaside, Oregon; (503) 738-9551.

**FAMILY PRACTITIONER.** San Ysidro Health Center, a comprehensive multispecialty clinic in south San Diego County, seeks a Family Practitioner for full-time out-patient work. Competitive salary. Excellent benefits. Respond to Number 23, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

**OB/GYN.** San Ysidro Health Center, a comprehensive multispecialty clinic in south San Diego County, seeks an OB/GYN to join the two current ones for full-time in-patient and out-patient work. We see a wide variety of clinical problems. Competitive salary. Excellent benefits. Respond to Number 24, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

**FAMILY PRACTICE PHYSICIAN** wanted for medical office, no OB/PED. Outstanding northwest medical community with many opportunities. Will introduce, reasonable price and terms. Unlimited outdoor activities. Reply to Number 22, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

**FAMILY PRACTITIONER.** Multispecialty Group of 31 physicians has immediate positions available for Board certified or eligible Family Practitioner. The growth oriented Group is located on the California coast, 60 miles north of Los Angeles. Guaranteed salary plus incentives. No investment required. City is a great place to raise a family in a clean environment. Send résumés to: Recruitment Physician, 2705 Loma Vista Rd., Ventura, CA 93003.

## SAN DIEGO

Busy, multispecialty group in San Diego is expanding and will be adding Specialists and Family Physicians to its staff. Outstanding practice opportunities in an ideal geographic setting. For immediate consideration, please send CV to: Miriam Stephens, Director of Professional Recruitment, SMITH HANNA Medical Group, 5703 Oberlin Dr., Ste. 302-49, San Diego, CA 92121.

**DIRECTOR OF HEALTH & COUNSELING SERVICES** for California State University, Sacramento. California Medical License required, Board certification in medical specialty with three years experience, particularly working with young adults; administrative experience in ambulatory care facility, knowledge of personnel and budget management. Salary and benefits competitive. Send résumé and three references to: Personnel Office, CSU, Sacramento, 6000 J St., Sacramento, CA 95819. Deadline: May 1, 1987. CSU, Sacramento is an Affirmative Action/Equal Opportunity Employer.

**OPHTHALMOLOGIST**—Multispecialty family care oriented group needs additional Ophthalmologist. Excellent practice opportunity in a dynamic Southwest city; good benefits and salary plan. Send CV to: R. E. Sollenberger, Administrator, Tucson Medical Associates, Ltd., PO Box 26926, Tucson, AZ 85726.

**SAN DIEGO: FAMILY PRACTICE AND INTERNAL MEDICINE.** Several openings for Board certified FPs and IMs with rapidly growing, well-financed clinic. Unique private practice environment. Salary plus bonus. Contact Michele Manceau, 3702 Ruffin Rd., San Diego, CA 92123; (619) 560-4030.

**SACRAMENTO AREA—RADIOLOGY**—Interesting multi-office practice. Part-time and vacation coverage needed. Possible long term association. Robert Swisher, MD, (916) 786-9440. 729 Sunrise Ave.-901, Roseville, CA 95661.

**NORTHERN CALIFORNIA**: FP/IM physicians needed to staff ambulatory care clinics in the Central Valley region of California. Paid malpractice and excellent benefit package. Incentive plus guarantee. If interested, please contact SEMG, PO Box 214584, Sacramento, CA 95821.

**SAN FRANCISCO, FAMILY PRACTICE.** Busy, growing primary care practice needs BC/BE FP. Serves mid/lower income families, multi-cultural, multi-racial; members of several HMOs and PPOs. Spanish helpful. Contact Barbara Bishop, MD, 2517 San Bruno Ave., San Francisco, CA 94134; (415) 468-0250.

**NEAR STANFORD**—Six Internists, all sub-specialty trained and members of clinical faculty at Stanford, interested in an Associate with subspecialty interest and training. Should be well grounded in Internal Medicine. Send CV to: Dr. Bigler, El Camino Internal Medical Group, 125 South Dr., Mountain View, CA 94040.

**WASHINGTON—PUGET SOUND AREA.** Six person Family Practice Group in multispecialty clinic has opening for two BE/BC Family Practitioners. Obstetrics encouraged. Excellent practice opportunity with full range of fringe benefits. Please reply with CV to: William A. Latta. Administrator, 500 N. Lilly Rd., Olympia, WA 98506; (206) 456-1122.

**ORTHOPEDICS**—Multispecialty family care oriented group needs additional Orthopedic Physicians. Excellent practice opportunity in a dynamic Southwest city; good benefits and salary plan. Send CV to: R. E. Sollenberger, Administrator, Tucson Medical Associates, Ltd., PO Box 26926, Tucson, AZ 85726.

**SEATTLE AREA**—Neurologist, Orthopedist, ENT, wanted for multispecialty clinic in beautiful seaside community. Excellent lifestyle in growing area. Expense sharing with established group in new facility allows clinical practice without administrative demands. Reply with CV to: North Kitsap Medical Center, 20700 Bond Rd. N.E., Poulsbo, WA 98370.

**INTERNIST BC/BE**—Busy internal medicine/endocrinology group practice in central California seeks Internist to join. New graduates encouraged. Reply with CV to: PO Box 5716, Fresno, CA 93755-5716.

**PEDIATRICIAN BC/BE** for hospital-based teaching practice. Interest and training in neonatology and critical care pediatrics preferred. Join two full-time pediatricians and two full-time neonatologists in hospital with Level II ICN and busy inpatient and out-patient services. Paid malpractice. Salary negotiable based on training and experience. Submit CV and references to: Patricia A. Dixon, MD, Director, Pediatrics/Neonatal Services, San Joaquin General Hospital, PO Box 1020, Stockton, CA 95201; (209) 468-6600. AA/EOE.

**ENERGETIC PEDIATRICIAN WANTED** to join established practice in California, share overhead, introduce to patients and OB. Great opportunity for Pediatrician to build practice in Los Angeles/Burbank area. Reply (818) 843-6203.

**OB/GYN PACIFIC NORTHWEST**—beautiful country setting, easy access to urban amenities. Eight person group seeks second OB/GYN for rapidly growing, low-risk practice. Family oriented community near major urban area, 60 minutes from outstanding ski resort. For information call or send CV to: The Friedrich Group, Inc., 9284 Horncliff Northeast, Bainbridge Island, WA 98110, (206) 547-7850 or (206) 842-5248.

**INTERNIST—BE/BC.** San Diego Cardiologist seeking associate: recently trained Internist with interest in cardiology. Experienced in bedside invasive techniques: Swan-Ganz, Catheter and temporary pacemaker insertion. Send CV to: San Diego Heart & Medical Clinic, 3660 Clairemont Dr., Suite 6, San Diego, CA 91117; (619) 274-2560.

**TEXAS,** opportunity for a committed, energetic F/P, G/P, G/S, to practice in a lakeside community, in the Piney Woods area of east Texas. First year guarantee, etc. Send CV to Medical Support Services, 11509 Quarterhorse Trail, Austin, TX 78750 or call Armando L. Frezza, (512) 331-4164.

**SOUTHERN CALIFORNIA BEACH AREA,** female/male, BE/BC Am. graduate to join established OB/GYN. Guarantee plus malpractice insurance; some experience preferred. Please reply to Number 20, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

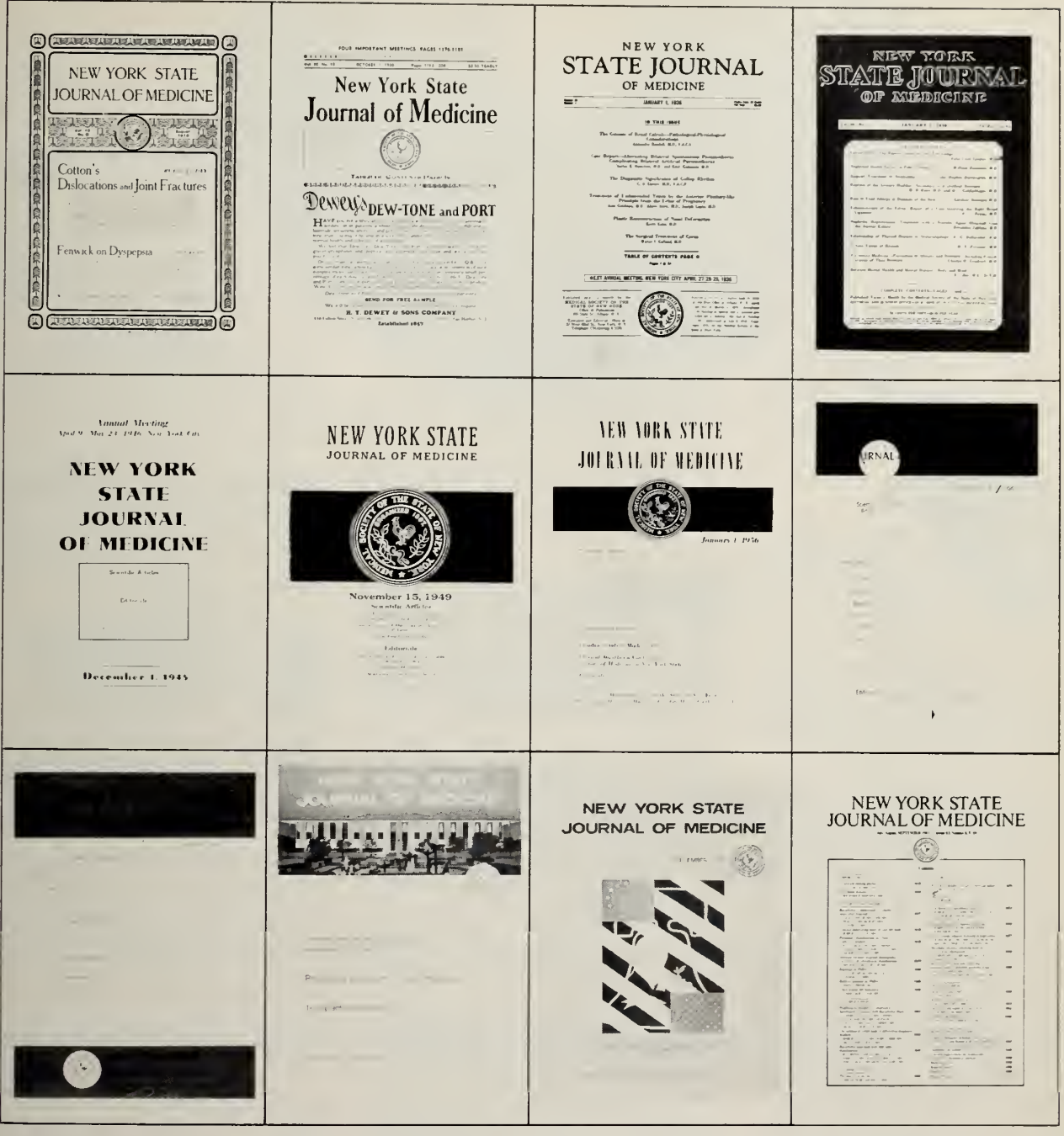
**OBSTETRICS AND GYNECOLOGY**—Multispecialty, family care oriented group has two excellent practice opportunities for OB/GYN specialists. We are located in a growing, dynamic Southwest city and offer an excellent benefit and incentive salary program. Send CV to R. E. Sollenberger, Administrator, Tucson Medical Associates, Ltd., PO Box 25926, Tucson, AZ 85726.

**PHYSICIAN—INTERNAL MEDICINE** needed to join Christian interdisciplinary health care team serving the whole person in community. Exciting, growing regional oncology and preventive medicine institute. Person must be traditionally trained, Board certified or eligible, have broad experience and interest in complimentary therapies. State-of-the-art equipment. Competitive salary commensurate with experience and training. Contact Dr Kenneth Bakken, Executive Director, Northwest Oncology Clinics, 901 Boren Ave., Ste. 901, Seattle, WA 98104; telephone (206) 292-2277.

**INTERNIST**—The community of Artesia, New Mexico is seeking an Internist to establish a solo practice. Cross-coverage available from local Internist. Community based financial assistance may be available for the right individual. Family-oriented community with year 'round recreation. Excellent weather. Fully equipped 38-bed new hospital. Submit CV to: Rita Longino, Southwest Community Health Services, PO Box 26666, Albuquerque, NM 87125-6666.

*(Continued on Page 528)*

# Cover to cover . . . . always good reading.




In 1986, the *New York State Journal of Medicine* promises to provide timely and stimulating commentary, challenging research papers, analysis of clinical trends, debate on topical issues, and in-depth coverage of medical news. The journal will make a welcome gift to a colleague or student in the United States or abroad.

A free copy of the July 1985 issue, a special issue on smoking, will be included with each subscription while the supply lasts.

SUBSCRIPTION ORDER FORM Clip and mail WJ4/87

**Circulation Department**
**New York State Journal of Medicine**
**420 Lakeville Rd., P.O. Box 5404, Lake Success, N.Y. 11042**

Name_____

Address_____

| | 1 Year | 2 Years | 3 Years |
|---|---|---|---|
| U.S. & Canada | ☐ $25 | ☐ $45 | ☐ $60 |
| Foreign | ☐ $30 | ☐ $55 | ☐ $75 |

*Payment required with order.*

(Continued from Page 526)

**INTERNIST:** Excellent opportunity for BE/BC Internist(s). Ground floor of integrated health system in desert community, 35 minutes from Palm Springs. Onsite hospital ancillary support, well established tertiary care facilities nearby. Excellent salary, benefits. Send CV to: Tom Schmidt, Professional Health Technologies, 915 Camino Del Mar, Del Mar, CA 92014.

**NEUROLOGY.** Position available with small, growth oriented neuro-musculo-rehabilitation clinic. Association with other Neurologist. Board certified/eligible. Excellent practice opportunity with practice costs paid. Superb living conditions on central California coast. Send CV to: David Graham, Administrator, Central Rehabilitation Clinic, Inc., 607 E. Plaza Dr., Ste. C-1, Santa Maria, CA 93454.

**OPHTHALMOLOGIST.** Private practice opportunity available in the community of Clovis, New Mexico. Financial assistance available for the right individual. Please submit CV to: Bill Norris, Southwest Community Health Services, PO Box 26666, Albuquerque, NM 87125-6666; or, call 1 (800) 545-4030, Ext. 8300 for further information.

**Western States**
**OPENINGS**

Several multispecialty groups and hospitals have asked us to recruit for over 200 positions of various specialties, **Western States Physician Services, 407 S. Clovis Ave., Suite 108, Fresno, CA 93727, (209) 252-3000.**

**OB/GYN BE/BC** for busy all woman private practice composed of one OB/GYN, one CNM and two NPs located in Berkeley/Oakland in beautiful Victorian office. Must be sensitive, well-trained, and personable. Please forward CV to: H. Modell, 5309 College Ave., Oakland, CA 94618 or call (415) 420-1200.

**PRACTICE FAMILY MEDICINE** with the people in rural Iowa communities where the quality of life is superb. Solo and group practice opportunities available including guaranteed salaries and full benefit packages. For an immediate response please call 1 (800) 247-3121, ext. 8204 (USA).

**PRIMARY CARE PHYSICIAN** needed for growing Woman's Health Center in San Francisco. Competitive performance based compensation. Malpractice provided. Contact Jeff M. Gerard at (415) 668-4005.

**INTERNAL MEDICINE**—Multispecialty group needs additional internists. A growing group in a dynamic Southwest community; excellent practice; benefits; and investment opportunities. Send CV to R. E. Sollenberger, Administrator, Tucson Medical Associates, Ltd, PO Box 26926, Tucson, AZ 85726.

**DERMATOLOGIST.** The community of Clovis, New Mexico is seeking a Dermatologist to establish a private practice. Financial assistance is available. For further information, please submit CV to: Bill Norris, Southwest Community Health Services, PO Box 26666, Albuquerque, NM 87125-6666.

**PEDIATRICIAN WANTED.** On Puget Sound 30 physician multispecialty clinic looking for BE/BC Pediatrician for established practice in our Pediatric Department. Community of 160,000 on beautiful Puget Sound just one hour from Seattle. Excellent salary plus bonus and fringes with early partnership. Contact or send CV to Administrator, The Doctors Clinic, 2512 Wheaton Way, Bremerton, WA 98310; (206) 478-6286.

**RADIOLOGIST,** semi-retired needed part-time to read office x-rays for large musculo-skeletal group in northern California. Interested physicians contact Number 25, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

**ASSISTANT PROGRAM DIRECTOR** or Faculty Person for Family Practice Program. Must have AAFP Boards. Would like private practice experience, but will evaluate applicant's overall strengths and will waive practice requirement in selected candidates. Strong program. University (University of California, Davis) affiliated. Excellent opportunities in research, curriculum development, and teaching of clinical skills. Call or send CV to Bruce Nickols, MD, Director of Family Practice, San Joaquin General Hospital, PO Box 1020, Stockton, CA 95201; (209) 468-6834. AA/EOE.

**FAMILY PHYSICIAN** for growing innovative family health center in San Francisco bay peninsula. Practice OB and newborn to geriatrics. No major surgery. Health education emphasis. Multidisciplinary team. POMR. Abundant education and teaching opportunity. Ideal living. ABFP certified residency preferred. Women applicants encouranged. EOE. Salary negotiable. Contact: J Hopkins, MD, 704 Webster, Palo Alto, CA 94301; (415) 324-1940.

**EXCELLENT TEXAS OPPORTUNITY,** for an OB/GYN and P/D person, to practice in a community close in to Houston, Texas. Enjoy country living at its best with the convenience of Houston nearby. First year guarantee, etc. Send C/V to, Medical Support Services, 11509 Quarterhorse Trail, Austin, TX 78750, or call Armando L. Frezza, (512) 331-4164.

**STUDENT HEALTH PHYSICIAN.** Join a staff of three MDs providing out-patient care at a University campus 48 miles north of San Francisco. Salary competitive. Direct applications and inquiries to Personnel, Sonoma State University, Rohnert Park, CA 94928. Apply by May 22, 1987 for first consideration. Call (707) 664-2166 (voice), (707) 664-2751 (TDD). AA/EOE.

**CALIFORNIA, SAN FRANCISCO BAY AREA**—A leading HMO near San Francisco, California is seeking Board prepared/certified Physicians to staff a busy, urban, full-service Emergency Department. Kaiser Permanente is a large, pre-paid Health Maintenance Organization offering a competitive salary, job security, shareholder status, and generous benefits including health care, life insurance, disability insurance, sick leave, and educational leave. Please address all inquiries to: Hans P. Odsen, MD, Chief, Emergency Department, Kaiser Permanente Medical Center, 1200 El Camino Real, South San Francisco, CA 94080; (415) 742-2513 or 2514.

**NEPHROLOGIST/INTERNIST.** Opening available in 160+ physician group. Need additional Nephrologist/Internist in a busy and fulfilling HMO practice in the San Francisco bay area. Excellent working conditions. Ample opportunities for house staff teaching, clinical faculty appointment, cooperative group participation. Competitive salary. Superb benefit package. Reply with CV to William Peters, MD, Department of Internal Medicine, The Permanente Medical Group, 260 International Circle, San Jose, CA 95119. An Equal Opportunity/Affirmative Action Employer.

**INTERNIST** or select medical subspecialist sought for private practice in Palo Alto, California. A unique opportunity for a well-qualified individual to affiliate with a small group of successful, experienced clinicians practicing independently in a university setting. Financial arrangements flexible. No investment required. Send résumé to PO Box 7132, Menlo Park, CA 94025.

**HEMATOLOGIST-ONCOLOGIST**—To join established multiethnic urban northern California private practice by August 1987. Second language of Mandarin, Cantonese, or Spanish necessary. Send CV and references. Please reply to Number 26, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

**LOCUM TENENS SERVICE**
**WESTERN PHYSICIANS REGISTRY**

*. . . offers coverage for vacation or continuing education. To arrange coverage for your practice or to participate as temporary physician, contact:* **Carol Sweig, Director, 1315 Evans Avenue, San Francisco, CA 94124; (415) 826-7676.**

## Advertise in the *Journal* and keep it confidential

For an extra $5.00 a month, we'll assign a confidential Reply Box number to your ad. We'll send the responses directly to you and we'll hold your box open for three months.

Send your ad to:
**The Western Journal of Medicine**
**PO Box 7602**
**San Francisco, CA 94120-7602.**

**CT-Utz-MR FELLOW** at UCLA-Harbor General Hospital looking for radiology position in Salt Lake City, Utah or vicinity. Available July 1, 1987. Send inquiries to Kyle Sutherland Hanks, MD, UCLA-Harbor General Hospital Box 334, 1000 W. Carson St., Torrance, CA 90509.

**PLASTIC SURGEON** completed residency and postgraduate training August 1986. Interviewing now. Prefer California, Utah, Oregon, Washington, Arizona. Please reply Number 21, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

**BOARD CERTIFIED OBSTETRICIAN-GYNECOLOGIST,** 46, seeking position in northern New Mexico, Albuquerque area. Prefer group practice. Please reply to Number 27, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

**OFFICE FOR SALE**—1,200 square feet located in Doctor's Village Medical Complex in beautiful Flagstaff, Arizona. This office is located within 2 blocks of the Flagstaff Medical Center and is perfect for a one man practice. Call (602) 779-5335, 9 am to 4 pm. Dr Michael J. Keberlein, 1360 North Rim Dr., Flagstaff, AZ 86001.

**GROWTH AREA OF SANTA CLARA VALLEY.** New medical office space for lease in the growth area of Silicon Valley . . . Morgan Hill, California. Easy hospital access, abundant parking, well located, generous tenant improvement allowances. Excellent referral sources for Family Practitioner, Pediatrician, and OB/GYN already in this newly available complex. Contact Dr Jon Hatakeyama, (408) 779-7391.

**OFFICE SPACE AVAILABLE.** New office condo in large complex; one hour from UCLA and Santa Barbara; 1,200 square feet with 2 surg. Additional 600 square feet optional for Psoriasis daycare, surg. recovery, or assoc. For sale, lease, lease/option. Call agent: Jim Higgins (805) 484-1600 or (805) 484-2744.

**CALIFORNIA:** IM, OB/GYN, Otolaryngology, Neurosurgery, Derm, Occupational Medicine, Family, Ophthal, Gastro, Surg, Allergy, Ortho, Psych, Pulm, Radiology, Rheum plus many others. Mary Bradshaw, Practice Broker/Recruiter, Valuations, 21 Altamount Dr., Orinda, CA 94563; (415) 376-0762.

(Continued on Page 530)

# right on TARGET

Consider a few features of **The Western Journal of Medicine:**

- **Epitomes of Progress** — Each month this section highlights the major advances in a different specialty with 15 or 20 brief epitomes by experts in the field.
- **Clinical Investigation** — Five major clinical research societies coordinate important new research findings, emphasizing clinical value.
- **Socioeconomics** — WJM is often the first to predict, examine and evaluate socioeconomic changes, trends.
- **Yearly Special Issue** — Each December's issue is devoted to a topic vital to physicians: clinical nutrition (1979), cost of care (1980), geriatrics (1981), occupational/environmental (1982), cross-cultural medicine (1983), personal health maintenance (1984), high-tech medicine (1985), medical informatics (1986).

WJ4/87

Enclosed is $_____ to cover _____ subscriptions.
Subscription renewal ☐ Regular subscription ☐
Foreign subscription ☐

TO: _____

Street _____

City/State/Zip _____

Specialty _____

Gift Card to read "From _____"

**The Western Journal of Medicine**

Please mail this coupon with enclosed payment to:

**Circulation Department**
P.O. Box 7602, San Francisco, California 94120-7602

Subscriptions, 12 issues Per Year
U.S. and Canada $30 1 year, $50 2 years

All other countries $50 1 year, $90 2 years

## PRACTICES AVAILABLE

**PALM SPRINGS AREA**—Active medical practice. No OB, Ped, Surg. Two hospitals opened to qualified MD—year-round golf, tennis, sunshine. Gross near 200K for 24 hr/week. Potential unlimited for aggressive MD. $25,000 down and easy terms. Excellent lease. Reply to Number 7, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

**THIRTY-YEAR-OLD FAMILY PRACTICE** for sale. "Silicon Valley's Finest." Approximately 1,000 active patient charts. Mix of 70% private, 30% (over 65). Complete practice and furnishings. Great location in heart of Silicon Valley. Excellent assumable lease. Contact Bugati Royale, 300 Third St., Ste. 4, Los Altos, CA 94022 or call (415) 941-5500.

**FOR SALE. WELL ESTABLISHED,** medium size Pediatric practice, San Joaquin Valley foothills, easy access to Los Angeles and San Francisco. Growing community, good opportunity to expand. Financing available. Office located adjacent to hospital. Coverage shared with two Pediatricians. Excellent referral base. Local hospital affiliated with major medical centers in Los Angeles and Fresno. Owner retiring, will introduce. Contact Number 16, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

**INTERNAL MEDICINE.** Scenic NW private practice opportunity. Five minutes from two excellent hospitals. Gross 200 K+. Date and terms negotiable. Please reply Number 19, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

**FOR SALE**—Pediatric practice in a rapidly growing University town of 37,000. Only two Pediatricians. Practice is only two years old but already grossing $100,000 plus. Excellent potentials. Easy terms. Call (209) 668-7195.

**CALIFORNIA, MONTEREY BAY AREA PEDIATRIC PRACTICE** for sale. Share call with three Board certified Pediatricians. Walk to hospital with level II Nursery. Office equipment and furnishings included. Established 11 years, retiring for health reasons. Call (408) 728-4223 evenings.

**FAMILY PRACTICE PHYSICIAN** wanted for medical office, no OB/PED. Outstanding northwest medical community with many opportunities. Will introduce, reasonable price and terms. Unlimited outdoor activies. Reply to Number 22, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

**FAMILY PRACTICE-GENERAL SURGERY.** Multiple practice situation, long established. Prime Orange County, California beach city location. Adjacent to modern hospital with ICU/CCU. Includes equipment, assumable lease. Reply to Number 17, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

**FOR SALE ESTABLISHED NEUROLOGY PRACTICE,** 40 miles south of Seattle next to major adult and ped. hospital. CT, MRI available; share call. EEG, EMG, evoked potentials in office. Gross $280K, sell $60K plus acct. rec. (if desired), financing available. Available 1987, retire for health reasons and available during transition. Call (206) 572-8663, leave name and phone. Will return call after hours.

**FAMILY PRACTICE.** 30 years in Torrance, California area. Great potential; ideal office with boulevard exposure and visibility. Low rent. Seller available to work up to 10 hours/week, (213) 323-2293.

**GYN/INF PRACTICE FOR SALE.** OB can be developed easily. Available immediately for 1 or 2 OB/GYNS. 13 years in development. Will introduce. Beautiful southern Oregon with fully equipped office near hospital. For information write: "Practice Sale," 853 Spring St., Medford, OR 97504.

## MEDICAL EQUIPMENT

**50% OFF** previously owned medical, laboratory, office, x-ray, ultra-sound equipment in excellent condition. We buy, sell, broker and repair. Office appraisals by Certified Surgical Consultants. Call Medical Equipment Resale, Inc., 24026 Haggerty Rd., Farmington Hills, MI 48018; (313) 477-6880 anytime.

**LASER FOR SALE**—Coherent Model 450 surgical $CO_2$, 25 watts, excellent condition. $18,500. ENT, gastro. attachments available. Other medical lasers purchased, sold. Moorpark Electro-optics, Inc. (805) 529-1649.

**COMPLETE SET-UPS TO SINGLE ITEMS**
Save on your medical equipment needs by buying quality used instead of new! Burdick EK-8 like new 1150, Ritter power tables #75—$3,000, Coulter S+ cell counter, Ames Seralyzers #5110A— $500, Ames Seralyzers #5181 (like new) $1,500, Neurology equipment-Grass 17 chan EEG, Grass 4 chan. Evoke Potential, Teca TE-4 with computer all for $21,500. Duodenoscope, Colonoscope, Gastroscope all by Olympus, Wolfe Laparoscope, Alpha Bio-Feedback Chamber (like new), Toshiba 300 mas Portable X-Ray self-propelled $4,000. This is a partial, call or write for complete listing.
**MEDEXCHANGE (214) 369-3960**
**PO Box 18164, Dallas, TX 75218.**

## COMPUTER INFORMATION

**COMPUTERIZE YOUR BILLING**—Remarkably easy-to-use software automatically prints bills, statements, insurance forms. Menu-driven. Reports aging balances, referral sources, income by time period, procedure codes and more. Installs automatically. IBM and compatibles. Solo or group practice. Demonstration disk available. Call or write REM Systems, Inc., Dept. WJ4, 180 Emerson, Palo Alto, CA 94301; (415) 322-0369.

FREE INTRODUCTORY
MICROCOMPUTER DISK:
*Physicians' Educational Series*

**CONSULT-2**

*An Interactive Artificial Intelligence Program for DOS 2.0 or Higher*

Neither Copy-Righted nor Copy-Protected

**John H. Frenster, MD, FACP**
**247 Stockbridge Ave.**
**Atherton, CA 94025**

## PRACTICE WANTED

**I WANT TO BUY**—retiring/relocating? Family Practice/Urgent Care/Industrial Medicine by BC Family Practitioner with some ER/Surgical/Ortho skills. Prefer Bay Area/San Jose, LA/Rancho California, San Diego metro/suburbs. Others considered if promising. High net or potential. Rural considered, bilingual OK, prefer no Medi-Cal. Start soon or wait until you are ready! Consider also long-term locum tenens. Solo/partnership. Reply Box 613, Osseo, MN 55369; (612) 424-9441.

## SEMINARS

**ADVANCED ECHOCARDIOGRAPHY AND DOPPLER ULTRASOUND 1987**
**June 11-13, 1987, San Diego, California**
Fees: $385 for ACC members; $450 for non-members; $295 for residents, fellows in training (with verification), nurses and technicians. 21 Category 1 credit. **For information contact:** American College of Cardiology, (800) 253-4636. In Maryland and Alaska, (301) 897-5400, ext. 226.

## SEMINARS

**CONSULTATIVE CARDIOLOGY: Update in Diagnostic and Therapeutic Techniques**
**June 25-27, 1987, Newport Beach, California**
Fees: $300 for ACC members; $355 for non-members; $200 for residents, fellows in training, nurses and technicians. 14 Category 1 credit. Information, contact: American College of Cardiology, (800) 253-4636. In Maryland or Alaska, (301) 897-5400, ext. 226.

## MISCELLANEOUS

**FOR SALE:** Mountain home N-Star at Tahoe. 5 bedrooms, 3½ baths, all year access. 5,280 square feet living space, 5 fireplaces, 2 furnaces, double garage, loft. M. L. Trewin, 1617 Broadway, Vallejo, CA 94589; (707) 552-9247.

**SAN DIEGO AREA**—Beautiful 6,000 square foot home with 5 bedrooms and maid's quarters, pool, orchard and horse corral on 3 acres. $850,000 Susan/Plaza Properties, (619) 436-6188.

***MEDICAL SPANISH — EASY!***
Speak to patients in everyday Spanish.
*Complete 6-cassette course with manual/dictionary, pocket guide. All basic terms and procedures: $95 plus tax
RESULTS GUARANTEED OR MONEY REFUNDED!
**CALL/WRITE FOR FACTS ON OTHER MATERIALS, FREE MEDICAL SPANISH NEWSLETTER!**
CSLA
**CALIFORNIA SPANISH LANGUAGE ASSOC.**
**P.O. Box 3522-J, San Diego, CA 92073-0590**
**(619) 544-0548**

*Ads Get Results!*

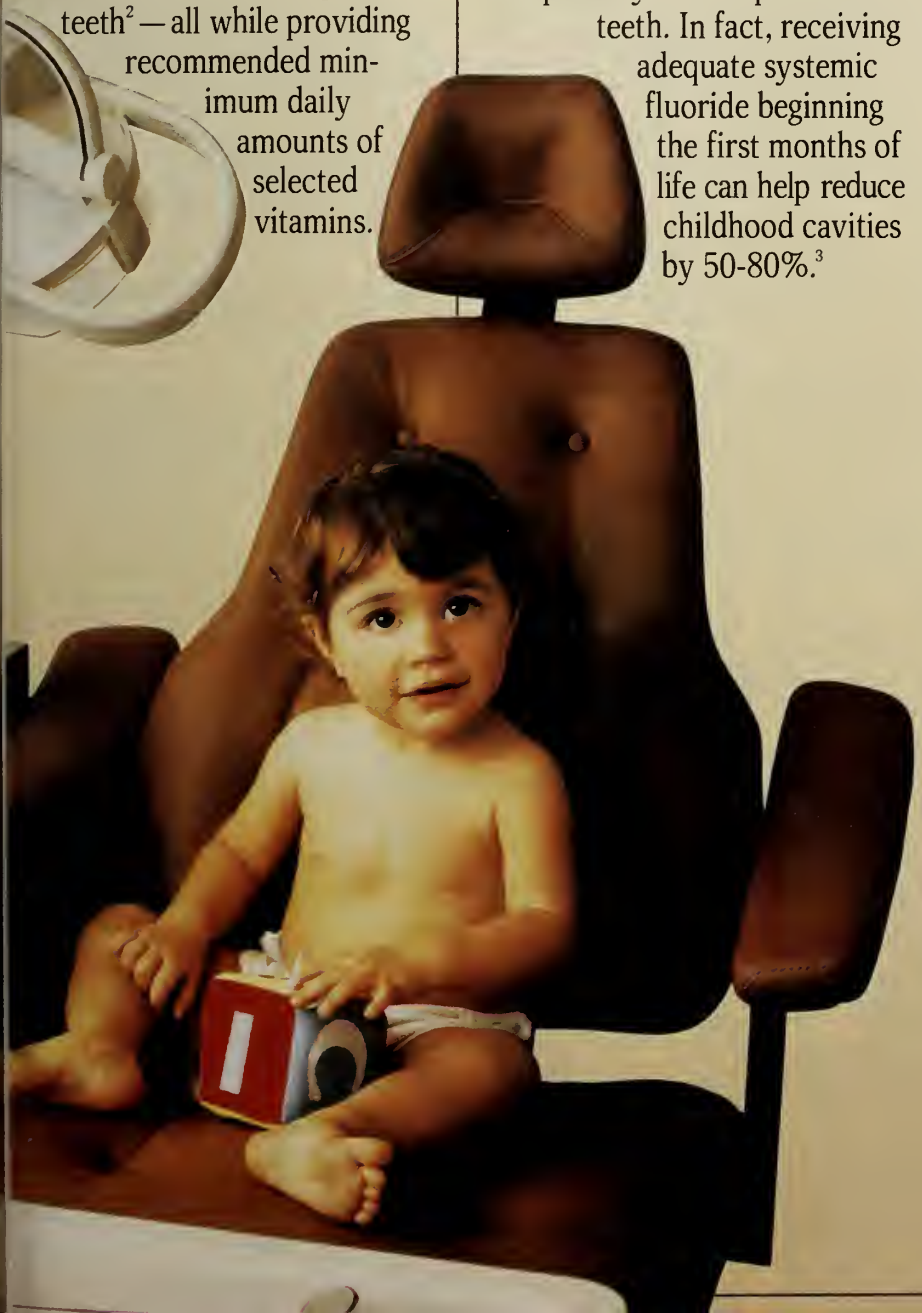
CLASSIFIED
INFORMATION
**(415) 863-5522**
**EXTENSION 244**

# Your prescription now...

# for a lifetime of happy dental visits

**During the first months of life,** Vi-Flor® vitamin-fluoride supplements begin to enhance tooth morphology,[1] increase enamel hardness, and promote mineralization of unerupted teeth[2]—all while providing recommended minimum daily amounts of selected vitamins.

**Fluoride supplementation is both prophylactic *and* therapeutic,** especially with newborns who are already in the process of developing 20 primary and 32 permanent teeth. In fact, receiving adequate systemic fluoride beginning the first months of life can help reduce childhood cavities by 50-80%.[3]



And that *daily* use through age 16 results in optimal levels of fluoride supplementation, for a lifetime of stronger teeth and lower-cost dental care.

## Prescribe

Vi-Flor® vitamin-fluoride supplements... now.
The essential first step begins with you, and...

**TRI·VI·FLOR®**
**POLY·VI·FLOR®**

**References:**

1. Moss SJ: The worldwide decline in caries prevention, in Mead Johnson Clinical Report Series, Clinical Importance of Fluoride Nutrition in Infants, Children, and Young Adults. Chicago, Pragmaton® 1985, Number 1, p. 2.

2. Newbrun E: How fluoride works: Topical vs. systemic action, in Mead Johnson Clinical Report Series, Clinical Importance of Fluoride Nutrition in Infants, Children, and Young Adults. Chicago, Pragmaton® 1985, Number 1, p. 5.

3. Aasenden R and Peebles T: Effects of fluoride supplementation from birth on human deciduous and permanent teeth. *Arch Oral Biol* 1974;19:321.

Mead Johnson
NUTRITIONAL DIVISION

© 1987 Bristol-Myers U.S. Pharmaceutical and Nutritional Group • Evansville, Indiana 47721 U.S.A.

L-K244-1-87

# Routine VI-FLOR® supplementation

**to help you guard appropriate patients against caries risk and nutritional risk.**

INDICATIONS AND USAGE: Prophylaxis of vitamin deficiencies and dental caries in children and adults when fluoride of water supply does not exceed 0.7 ppm.[1,2,3] And, in the case of TRI-VI-FLOR® 0.25 mg Drops with Iron and POLY-VI-FLOR® Drops and Chewable Tablets with Iron, prophylaxis against iron deficiencies. Note: VI-FLOR Drops do not contain folic acid because the vitamin is not stable in liquid form.

PRECAUTIONS: Do not exceed recommended dose or give concurrently with other medications containing significant amounts of fluoride. Prolonged excessive fluoride intake may cause dental fluorosis. All VI-FLOR® with Iron products: as with all products containing iron, parents should be warned against excessive dosage. The bottle should be kept out of reach of children.

Keep all VI-FLOR with Iron products tightly closed and away from direct light.

VI-FLOR Drops should be dispensed in the original plastic container, since contact with glass leads to instability and precipitation.

ADVERSE REACTIONS: Allergic rash has rarely been reported.

DOSAGE AND ADMINISTRATION:
Supplemental Fluoride Dosage Schedule (mg/day)*

| Age | Concentration of Fluoride in Drinking Water (ppm) | | |
|---|---|---|---|
| | <0.3 | 0.3-0.7 | >0.7 |
| 2-wk-2 yr** | 0.25 | 0 | 0 |
| 2-3 yr | 0.5 | 0.25 | 0 |
| 3-16 yr | 1.0 | 0.5 | 0 |

*From the American Academy of Pediatrics Committee on Nutrition statement. Fluoride Supplementation: Revised Dosage Schedule. *Pediatrics* 63(1):150-152, 1979.
**The Committee favors initiating fluoride supplementation shortly after birth in breast-fed infants (0.25 mg F/day). In formula-fed infants, fluoride supplementation should be according to the fluoride content of the water used to prepare formula.

| PRODUCT | FORM | SIZE | FLUORIDE mg/dose |
|---|---|---|---|
| POLY-VI-FLOR 0.25 mg | Drops | 50 ml Bottle | 0.25 |
| POLY-VI-FLOR 0.25 mg with Iron | Drops | 50 ml Bottle | 0.25 |
| POLY-VI-FLOR 0.25 mg | Tablets | Bottle of 100 | 0.25 |
| POLY-VI-FLOR 0.25 mg with Iron | Tablets | Bottle of 100 | 0.25 |
| POLY-VI-FLOR 0.5 mg | Drops | 50 ml Bottle | 0.5 |
| POLY-VI-FLOR 0.5 mg with Iron | Drops | 50 ml Bottle | 0.5 |
| POLY-VI-FLOR 0.5 mg | Tablets | Bottle of 100 | 0.5 |
| POLY-VI-FLOR 0.5 mg with Iron | Tablets | Bottle of 100 | 0.5 |
| POLY-VI-FLOR 1.0 mg | Tablets | Bottle of 100 | 1.0 |
| POLY-VI-FLOR 1.0 mg with Iron | Tablets | Bottle of 100 | 1.0 |
| TRI-VI-FLOR 0.25 mg | Drops | 50 ml Bottle | 0.25 |
| TRI-VI-FLOR 0.25 mg with Iron | Drops | 50 ml Bottle | 0.25 |
| TRI-VI-FLOR 0.5 mg | Drops | 50 ml Bottle | 0.5 |
| TRI-VI-FLOR 1.0 mg | Tablets | Bottle of 100 | 1.0 |

REFERENCES:
1. Hennon DK, Stookey GK and Muhler JC: The Clinical Anticariogenic Effectiveness of Supplementary Fluoride-Vitamin Preparations—Results at the End of Four Years. *J Dentistry for Children* 34:439-443 (Nov) 1967.
2. Hennon DK, Stookey GK and Muhler JC: The Clinical Anticariogenic Effectiveness of Supplementary Fluoride-Vitamin Preparations—Results at the End of Five and a Half Years. *Pharmacology and Therapeutics in Dentistry* 1:1-6 (Oct) 1970.
3. Hennon DK, Stookey GK and Muhler JC: Prophylaxis of Dental Caries: Relative Effectiveness of Chewable Fluoride Preparations With and Without Added Vitamins. *J Pediatrics* 80:1018-1021 (June) 1972.

**VI-SOL®/VI-FLOR® products are the nation's most prescribed children's vitamin and vitamin-fluoride supplements.**

(For complete details, please consult full prescribing information.)

Mead Johnson
NUTRITIONAL DIVISION


# In Memoriam

*(Continued from Page 513)*

MARCHESI, JOHN C., Los Gatos. Died Dec 16, 1986, aged 64. Graduate of University of Illinois, Chicago, 1948. Licensed in California in 1949. Dr Marchesi was a member of the Santa Clara County Medical Society.

MASTELLOS, CHRISTOPHER, Norco. Died Dec 13, 1986, aged 61. Graduate of University of California, Irvine, California College of Medicine, 1962. Dr Mastellos was a member of the Riverside County Medical Association.

NELSON, CLARENCE E., Loma Linda. Died Dec 22, 1986, aged 91. Graduate of Loma Linda University, 1918. Licensed in California in 1918. Dr Nelson was a member of the Los Angeles County Medical Association.

NESSELBUSH, ORVAL P., Sacramento. Died Sep 4, 1986, aged 69. Graduate of University of Nebraska College of Medicine, Omaha, 1958. Licensed in California in 1959. Dr Nesselbush was a member of the Sacramento-El Dorado Medical Society.

NORGARD, MILTON C. Died Jan 22, 1987, aged 90. Graduate of University of California, Irvine, 1929. Dr Norgard was a member of the Los Angeles County Medical Association.

PAYNE, ROBERT W., Redwood City. Died Dec 11, 1986, aged 62. Graduate of Long Island College of Medicine, 1949. Licensed in California in 1953. Dr Payne was a member of the San Mateo County Medical Society.

PERLSTEIN, MINNIE O., Campbell. Died Dec 17, 1986, aged 81. Graduate of Rush Medical College, Chicago, 1928. Licensed in California in 1952. Dr. Perlstein was a member of the Santa Clara County Medical Society.

PRIEST, ETHEL H., Napa. Died Nov 7, 1986, aged 94. Graduate of University of Colorado, Denver, 1919. Dr Priest was a member of the Napa County Medical Society.

ROHLFING, WALTER A., Fresno. Died Dec 1, 1986, aged 68. Graduate of Washington University, St Louis, 1943. Licensed in California in 1946. Dr Rohlfing was a member of the Fresno-Madera Medical Society.

ROWE, WILLIAM W. Died Nov 1986, aged 71. Graduate of University of California, Irvine. Dr Rowe was a member of the Los Angeles County Medical Association.

SCHANTZ, GUY, Sonoma. Died Dec 14, 1986, aged 43. Graduate of University of Kansas, Kansas City, 1969. Licensed in California in 1971. Dr Schantz was a member of the Sonoma County Medical Association.

SCHMITT, HUGO H. Died Dec 9, 1986, aged 92. Graduate of Julius Maximilius, Würzburg, Germany, 1921. Licensed in California in 1924. Dr Schmitt was a member of the Santa Clara County Medical Society.

SCHWEMLEY, ROBERT G., Stockton. Died Sep 17, 1986, aged 53. Graduate of Ohio State University College of Medicine, Columbus, 1957. Licensed in California in 1961. Dr Schwemley was a member of the San Joaquin County Medical Society.

SHEPARD, RICHARD A. Died Nov 17, 1986, aged 80. Graduate of University of Illinois College of Medicine, Chicago, 1929. Licensed in California in 1947. Dr Shepard was a member of the Alameda-Contra Costa Medical Association.

SOOY, FRANCIS A., San Francisco. Died Sep 12, 1986, aged 71. Graduate of University of California, San Francisco, 1941. Licensed in California in 1941. Dr Sooy was a member of the San Francisco Medical Society.

THOMPSON, HARVEY E., Sacramento. Died Nov 13, 1986, aged 45. Graduate of University of Washington School of Medicine, Seattle, 1967. Licensed in California in 1976. Dr Thompson was a member of the Sacramento-El Dorado Medical Society.

TICHENOR, ERNEST I., Bakersfield. Died Oct 6, 1986, aged 83. Graduate of University of Oklahoma College of Medicine, Oklahoma City, 1933. Licensed in California in 1944. Dr Tichenor was a member of the Kern County Medical Society.

TICINOVICH, DAN A. Died Oct 12, 1986, aged 67. Graduate of Sveucilista University, Zagreb, 1943. Licensed in California in 1952. Dr Ticinovich was a member of the San Bernardino County Medical Society.

WALTER, RICHARD D., Los Angeles. Died Sep 27, 1986, aged 65. Graduate of St Louis University, 1946. Licensed in California in 1947. Dr Walter was a member of the Los Angeles County Medical Association.

WESTERBECK, CHARLES W., Playa del Rey. Died Oct 29, 1986, aged 62. Graduate of St Louis University School of Medicine, St Louis, 1947. Licensed in California in 1948. Dr Westerbeck was a member of the Los Angeles County Medical Association.

WHITSETT, JOHN W., Pasadena. Died Sep 10, 1986, aged 84. Graduate of Harvard Medical School, Boston, 1927. Dr Whitsett was a member of the Los Angeles County Medical Association.

WILSON, JAMES R., Los Angeles. Died Sep 30, 1986, aged 56. Graduate of Ohio State University College of Medicine, Columbus, 1956. Licensed in California in 1956. Dr Wilson was a member of the Los Angeles County Medical Association.

WITT, EVERETT J., La Canada. Died Sep 1, 1986, aged 75. Graduate of Rush Medical College, Chicago, 1941. Licensed in California in 1946. Dr Witt was a member of the Los Angeles County Medical Association.

WOLLACK, C. HAROLD, Fremont. Died Jul 19, 1986, aged 48. Graduate of George Washington University School of Medicine, Washington, DC, 1969. Licensed in California in 1970. Dr Wollack was a member of the Santa Clara County Medical Society.

WONG, DONALD LOY HUNG, La Mirada. Died Aug 31, 1986, aged 46. Graduate of UCLA School of Medicine, 1965. Licensed in California in 1966. Dr Wong was a member of the Los Angeles County Medical Association.

WONG, KENNETH, Santa Rosa. Died Oct 5, 1986, aged 62. Graduate of Loma Linda University, 1950. Licensed in California in 1950. Dr Wong was a member of the Sonoma County Medical Association.

YOUNG, WILLIAM ISAAC, Los Angeles. Died Nov 3, 1986, aged 38. Graduate of Case Western Reserve University School of Medicine, Cleveland, 1974. Licensed in California in 1977. Dr Young was a member of the Los Angeles County Medical Association.

The Western Journal of Medicine

SINCE 1902 • CIRCULATION 53,000+

# Classified Advertisements

The rate for each insertion is **$6 per line** (average six words per line) **with five line ($30) minimum.** Box number charge: $5 each month.

**Classified display rates $50 per inch.**

**Classified advertisements for commercial products or services—minimum charge $200.**

Copy for classified advertisements should be received not later than **25th of second month preceding issue. All copy must be typed or printed.** • Classified advertisers using Box Numbers forbid the disclosure of their identity; your inquiries in writing will be forwarded to Box Number advertisers. The right is reserved to reject or modify all classified advertising copy in conformity with the decisions of the Advertising Committee.

**Please Type or Print Advertising Copy**

**Classified Advertisements Are Payable in Advance**

CLASSIFIED ADVERTISING
THE WESTERN JOURNAL OF MEDICINE
P.O. BOX 7602, SAN FRANCISCO, CA 94120-7602

## ad copy

Print or Type Clearly

Number of lines _____ × $6 = $_____

Optional: Box charge: +$5 = _____

**Subtotal (minimum $35)** $_____

Number of insertions _____ × $_____ = (subtotal)

**Check enclosed for:** $_____

Name (Please Print)

Contact

Address

City/State/Zip

(_____)_____

Phone

Signature

## WESTERN STATE MEDICAL ASSOCIATIONS' MEETINGS

**Alaska State Medical Association**—2401 E 42nd Ave, Suite 104, Anchorage 99508. (907) 562-2662. Annual Meeting: June 3-7, 1987, Juneau.

**Arizona Medical Association, Inc**—810 W Bethany Home Rd, Phoenix 85013. (602) 246-8901. Annual Meeting: June 4-6, 1987, Pointe South Mountain, Phoenix.

**California Medical Association**—PO Box 7690, San Francisco 94120-7690. (415) 863-5522. Annual Meeting: March 4-9, 1988, Bally's Grand Hotel, Reno.

**Colorado Medical Society**—PO Box 17550, Denver 80217-0550. (303) 779-5455. Annual Meeting: September 9-12, 1987, Beaver Run, Breckenridge.

**Hawaii Medical Association**—320 Ward Ave, Suite 200, Honolulu 96814. (808) 536-7702. Annual Meeting: October 10-12, 1987, Kauai Surf, Kauai.

**Idaho Medical Association**—305 W Jefferson, PO Box 2668, Boise 83701. (208) 344-7888. Annual Meeting: July 27-August 2, 1987, Coeur d'Alene.

**Montana Medical Association**—2012 11th Ave, Suite 12, Helena 59601. (406) 443-4000. Interim Meeting: April 3-4, 1987, Colonial Inn, Helena.

**Nevada State Medical Association**—3660 Baker Lane, Reno 89502. (702) 825-6788. Annual Meeting: April 30-May 3, 1987, Ormsby House, Carson City.

**New Mexico Medical Society**—303 San Mateo NE, Suite 204, Albuquerque 87108. (505) 266-7868. Annual Meeting: May 6-8, 1987, Clarion Four Seasons, Albuquerque.

**Oregon Medical Association**—5210 SW Corbett Ave, Portland 97201. (503) 226-1555. Annual Meeting: (House of Delegates only): April 3-4, 1987, Salishan Lodge, Lincoln City.

**Utah State Medical Association**—540 E Fifth South, Salt Lake City 84102. (801) 355-7477. Annual Meeting: September 9-11, 1987, Westin Hotel Utah, Salt Lake City.

**Washington State Medical Association**—900 United Airlines Bldg, 2033 6th Ave, Seattle 98121. (206) 441-WSMA. Annual Meeting: September 17-20, 1987, Sheraton, Tacoma.

**Wyoming Medical Society**—PO Drawer 4009, Cheyenne 82003-4009. (307) 635-2424. Annual Meeting: June 25-29, 1987, Jackson Lake Lodge, Moran.

## ADVERTISING INDEX


ABBOTT LABORATORIES
*Depakote* . . . . . 511, 512

AUDIO DIGEST . . . . . 399

CIBA PHARMACEUTICALS
*Transderm-Nitro* . . . . . 395, 396

CLASSIFIED ADVERTISING . . . . . 525, 526, 528, 530

COOPERATIVE OF AMERICAN PHYSICIANS . . . . . 519

ELI LILLY & COMPANY
*Ceclor* . . . . . 410

GLAXO
*Trandate* . . . . . 522, 523, 524
*Zantac* . . . . . 421, 422

HOFFMANN-LA ROCHE LABORATORIES
*Dalmane* . . . . . 2nd cover, 393, 394
*Medication Education* . . . . . 517, 518
*Rocephin* . . . . . 3rd and 4th covers

MEAD JOHNSON & COMPANY
*Vi-Flor* . . . . . 531, 532

NEW YORK STATE JOURNAL OF MEDICINE . . . . . 527

PACIFIC PHYSICIAN SERVICES . . . . . 513

PHYSICIANS PRACTICE MANAGEMENT . . . . . 425

POSTGRADUATE MEDICINE . . . . . 396

PRINCETON PHARMACEUTICAL PRODUCTS
*Corgard* . . . . . 411, 412, 413, 414, 507, 508

A. H. ROBINS COMPANY
*Micro-K* . . . . . 404

SCHERING CORPORATION
*Normodyne* . . . . . 418, 419, 420

SMITHKLINE BECKMAN
*Dyazide* . . . . . 430

SOUTHERN CALIFORNIA PHYSICIANS
INSURANCE EXCHANGE . . . . . 415

E. R. SQUIBB & SONS
*Capoten* . . . . . 406, 407, 408

SYZYGY COMPUTER SYSTEMS, INC. . . . . 417

UNITED STATES AIR FORCE . . . . . 400

UNIVERSITY MICROFILM . . . . . 394

UPJOHN COMPANY
*Medrol* . . . . . 397
*Motrin* . . . . . 514, 515, 516
*Xanax* . . . . . 426, 427, 428

THE WESTERN JOURNAL OF MEDICINE
*Subscription Information* . . . . . 423, 529
*Special Issues Information* . . . . . 521

WILLIAMS, WRIGHT & ASSOCIATES, INC. . . . . 403

# Rocephin® IV·IM

## ceftriaxone sodium/Roche

**Before prescribing, please consult complete product information, a summary of which follows:**

*MICROBIOLOGY* The bactericidal activity of ceftriaxone results from inhibition of cell wall synthesis Ceftriaxone has a high degree of stability in the presence of beta lactamases, both penicillinases and cephalosporinases, of gram-negative and gram-positive bacteria Ceftriaxone is usually active against the following microorganisms *in vitro* and in clinical infections (see Indications and Usage)

*GRAM-NEGATIVE AEROBES Enterobacter aerogenes, Enterobacter cloacae, Escherichia coli, Haemophilus influenzae* (including ampicillin-resistant strains), *H parainfluenzae, Klebsiella* species (including *K pneumoniae*), *Neisseria gonorrhoeae* (including penicillinase and nonpenicillinase producing strains), *Neisseria meningitidis, Proteus mirabilis, Proteus vulgaris, Morganella morganii* and *Serratia marcescens*

Note Many strains of the above organisms that are multiply resistant to other antibiotics, e g , penicillins, cephalosporins and aminoglycosides, are susceptible to ceftriaxone sodium

Ceftriaxone is also active against many strains of *Pseudomonas aeruginosa*

*GRAM POSITIVE AEROBES Staphylococcus aureus* (including penicillinase producing strains) and *Staphylococcus epidermidis* (Note methicillin-resistant staphylococci are resistant to cephalosporins, including ceftriaxone), *Streptococcus pyogenes* (Group A beta-hemolytic streptococci), *Streptococcus agalactiae* (Group B streptococci) and *Streptococcus pneumoniae* (Note Most strains of enterococci, *Streptococcus faecalis* and Group D streptococci are resistant )

Ceftriaxone also demonstrates *in vitro* activity against the following microorganisms, although the clinical significance is unknown

*GRAM NEGATIVE AEROBES Citrobacter freundii, Citrobacter diversus, Providencia* species (including *Providencia rettgeri*), *Salmonella* species (including *S typhi*), *Shigella* species and *Acinetobacter calcoaceticus*

*ANAEROBES Bacteroides* species, *Clostridium* species (Note most strains of *C difficile* are resistant)

*SUSCEPTIBILITY TESTING* Standard susceptibility disk method Quantitative methods that require measurement of zone diameters give the most precise estimate of antibiotic susceptibility One such procedure (Bauer AW, Kirby WMM, Sherris JC, Turck M Antibiotic Susceptibility Testing by a Standardized Single Disk Method, *Am J Clin Pathol* 45 493-496, 1966, Standardized Disk Susceptibility Test *Federal Register* 39 19182 19184, 1974, National Committee for Clinical Laboratory Standards, Approved Standard ASM 2, Performance Standards for Antimicrobial Disk Susceptibility Tests, July 1975 ) has been recommended for use with disks to test susceptibility to ceftriaxone

Laboratory results of the standardized single-disk susceptibility test using a 30-mcg ceftriaxone disk should be interpreted according to the following three criteria

1 Susceptible organisms produce zones of 18 mm or greater, indicating that the tested organism is likely to respond to therapy
2 Organisms that produce zones of 14 to 17 mm are expected to be susceptible if a high dosage (not to exceed 4 gm per day) is used or if the infection is confined to tissues and fluids (e g , urine), in which high antibiotic levels are attained
3 Resistant organisms produce zones of 13 mm or less, indicating that other therapy should be selected

Organisms should be tested with the ceftriaxone disk since ceftriaxone has been shown by *in vitro* tests to be active against certain strains found resistant to cephalosporin class disks

Organisms having zones of less than 18 mm around the cephalothin disk are not necessarily of intermediate susceptibility or resistant to ceftriaxone

Standardized procedures require use of control organisms The 30-mcg ceftriaxone disk should give zone diameters between 29 and 35 mm, 22 and 28 mm and 17 and 23 mm for the reference strains *E coli* ATCC 25922, *S aureus* ATCC 25923 and *P aeruginosa* ATCC 27853, respectively

*DILUTION TECHNIQUES* Based on the pharmacokinetic profile of ceftriaxone, a bacterial isolate may be considered susceptible if the MIC value for ceftriaxone is not more than 16 mcg/ml Organisms are considered resistant to ceftriaxone if the MIC is equal to or greater than 64 mcg/ml Organisms having an MIC value of less than 64 mcg/ml, but greater than 16 mcg/ml, are expected to be susceptible if a high dosage (not to exceed 4 gm per day) is used or if the infection is confined to tissues and fluids (e g , urine), in which high antibiotic levels are attained

*E coli* ATCC 25922, *S aureus* ATCC 25923 and *P aeruginosa* ATCC 27853 are also the recommended reference strains for controlling ceftriaxone dilution tests Greater than 95% of MICs for the *E coli* strain should fall within the range of 0 016 to 0 5 mcg/ml The range for the *S aureus* strain should be 1 to 2 mcg/ml, while for the *P aeruginosa* strain the range should be 8 to 64 mcg/ml

**INDICATIONS AND USAGE:** Rocephin is indicated for the treatment of the following infections when caused by susceptible organisms

*LOWER RESPIRATORY TRACT INFECTIONS* caused by *Strep pneumoniae, Streptococcus* species (excluding enterococci), *Staph aureus, H influenzae, H parainfluenzae, Klebsiella* species (including *K pneumoniae*), *E coli, E aerogenes, Proteus mirabilis* and *Serratia marcescens*

*SKIN AND SKIN STRUCTURE INFECTIONS* caused by *Staph aureus, Staph epidermidis, Streptococcus* species (excluding enterococci), *E cloacae, Klebsiella* species (including *K pneumoniae*), *Proteus mirabilis* and *Pseudomonas aeruginosa*

*URINARY TRACT INFECTIONS (complicated and uncomplicated)* caused by *E coli, Proteus mirabilis, Proteus vulgaris, M morganii* and *Klebsiella* species (including *K pneumoniae*)

*UNCOMPLICATED GONORRHEA (cervical/urethral and rectal)* caused by *Neisseria gonorrhoeae*, including both penicillinase and nonpenicillinase producing strains

*PELVIC INFLAMMATORY DISEASE* caused by *N gonorrhoeae*

*BACTERIAL SEPTICEMIA* caused by *Staph aureus, Strep pneumoniae, E coli, H influenzae* and *K pneumoniae*

*BONE AND JOINT INFECTIONS* caused by *Staph aureus*, Strep *pneumoniae*, *Streptococcus* species (excluding enterococci), *E coli, P mirabilis, K pneumoniae* and *Enterobacter* species

*INTRA-ABDOMINAL INFECTIONS* caused by *E coli* and *K pneumoniae*

*MENINGITIS* caused by *H influenzae, N meningitidis* and *Strep pneumoniae* Ceftriaxone has also been used successfully in a limited number of cases of meningitis and shunt infections caused by *Staph epidermidis* and *E coli*

*PROPHYLAXIS* The administration of a single dose of ceftriaxone preoperatively may reduce the incidence of postoperative infections in patients undergoing coronary artery bypass surgery

Although ceftriaxone has been shown to have been as effective as cefazolin in the prevention of infection following coronary artery bypass surgery, no placebo-controlled trials have been conducted to evaluate any cephalosporin antibiotic in the prevention of infection following coronary artery bypass surgery

*SUSCEPTIBILITY TESTING* Before instituting treatment with Rocephin, appropriate specimens should be obtained for isolation of the causative organism and for determination of its susceptibility to the drug Therapy may be instituted prior to obtaining results of susceptibility testing

**CONTRAINDICATIONS:** Rocephin is contraindicated in patients with known allergy to the cephalosporin class of antibiotics

**WARNINGS:** BEFORE THERAPY WITH ROCEPHIN IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE TO DETERMINE WHETHER THE PATIENT HAS HAD PREVIOUS HYPERSENSITIVITY REACTIONS TO CEPHALOSPORINS, PENICILLINS OR OTHER DRUGS. THIS PRODUCT SHOULD BE GIVEN CAUTIOUSLY TO PENICILLIN-SENSITIVE PATIENTS. ANTIBIOTICS SHOULD BE ADMINISTERED WITH CAUTION TO ANY PATIENT WHO HAS DEMONSTRATED SOME FORM OF ALLERGY, PARTICULARLY TO DRUGS. SERIOUS ACUTE HYPERSENSITIVITY REACTIONS MAY REQUIRE THE USE OF SUBCUTANEOUS EPINEPHRINE AND OTHER EMERGENCY MEASURES

Pseudomembranous colitis has been reported with the use of cephalosporins (and other broad spectrum antibiotics), therefore, it is important to consider its diagnosis in patients who develop diarrhea in association with antibiotic use

**ROCEPHIN® (ceftriaxone sodium/Roche)**

Treatment with broad spectrum antibiotics alters the normal flora of the colon and may permit overgrowth of clostridia Studies indicate a toxin produced by *Clostridium difficile* is one primary cause of antibiotic associated colitis Cholestyramine and colestipol resins have been shown to bind to the toxin in vitro

Mild cases of colitis respond to drug discontinuance alone Moderate to severe cases should be managed with fluid, electrolyte and protein supplementation as indicated

When the colitis is not relieved by drug discontinuance or when it is severe, oral vancomycin is the treatment of choice for antibiotic associated pseudomembranous colitis produced by *C difficile* Other causes of colitis should also be considered

**PRECAUTIONS** *GENERAL* Although transient elevations of BUN and serum creatinine have been observed, at the recommended dosages, the nephrotoxic potential of Rocephin is similar to that of other cephalosporins

Ceftriaxone is excreted via both biliary and renal excretion (see Clinical Pharmacology) Therefore patients with renal failure normally require no adjustment in dosage when usual doses of Rocephin are administered, but concentrations of drug in the serum should be monitored periodically If evidence of accumulation exists, dosage should be decreased accordingly

Dosage adjustments should not be necessary in patients with hepatic dysfunction, however, in patients with both hepatic dysfunction and significant renal disease, Rocephin dosage should not exceed 2 gm daily without close monitoring of serum concentrations

Alterations in prothrombin times have occurred rarely in patients treated with Rocephin Patients with impaired vitamin K synthesis or low vitamin K stores (e g , chronic hepatic disease and malnutrition) may require monitoring of prothrombin time during Rocephin treatment Vitamin K administration (10 mg weekly) may be necessary if the prothrombin time is prolonged before or during therapy

Prolonged use of Rocephin may result in overgrowth of nonsusceptible organisms Careful observation of the patient is essential If superinfection occurs during therapy appropriate measures should be taken

Rocephin should be prescribed with caution in individuals with a history of gastrointestinal disease, especially colitis

*CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY* Carcinogenesis Considering the maximum duration of treatment and the class of the compound, carcinogenicity studies with ceftriaxone in animals have not been performed The maximum duration of animal toxicity studies was six months

Mutagenesis Genetic toxicology tests included the Ames test, a micronucleus test and a test for chromosomal aberrations in human lymphocytes cultured *in vitro* with ceftriaxone Ceftriaxone showed no potential for mutagenic activity in these studies

Impairment of Fertility Ceftriaxone produced no impairment of fertility when given intravenously to rats at daily doses up to 586 mg/kg/day, approximately 20 times the recommended clinical dose of 2 gm/day

*PREGNANCY* Teratogenic Effects Pregnancy Category B Reproductive studies have been performed in mice and rats at doses up to 20 times the usual human dose and have no evidence of embryotoxicity, fetotoxicity or teratogenicity In primates, no embryotoxicity or teratogenicity was demonstrated at a dose approximately three times the human dose

There are, however, no adequate and well-controlled studies in pregnant women Because animal reproductive studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed

Nonteratogenic Effects In rats, in the Segment I (fertility and general reproduction) and Segment III (perinatal and postnatal) studies with intravenously administered ceftriaxone, no adverse effects were noted on various reproductive parameters during gestation and lactation, including postnatal growth, functional behavior and reproductive ability of the offspring, at doses of 586 mg/kg/day or less

*NURSING MOTHERS* Low concentrations of ceftriaxone are excreted in human milk Caution should be exercised when Rocephin is administered to a nursing woman

*PEDIATRIC USE* Safety and effectiveness of Rocephin in neonates, infants and children have been established for the dosages described in the Dosage and Administration section

**ADVERSE REACTIONS:** Rocephin is generally well tolerated In clinical trials, the following adverse reactions, which were considered to be related to Rocephin therapy or of uncertain etiology, were observed

*LOCAL REACTIONS* – pain, induration or tenderness at the site of injection (1%) Less frequently reported (less than 1%) was phlebitis after IV administration

*HYPERSENSITIVITY* – rash (1 7%) Less frequently reported (less than 1%) were pruritus, fever or chills

*HEMATOLOGIC* – eosinophilia (6%), thrombocytosis (5 1%) and leukopenia (2 1%) Less frequently reported (less than 1%) were anemia, neutropenia, lymphopenia, thrombocytopenia and prolongation of the prothrombin time

*GASTROINTESTINAL* – diarrhea (2 7%) Less frequently reported (less than 1%) were nausea or vomiting, and dysgeusia

*HEPATIC* – elevations of SGOT (3 1%) or SGPT (3 3%) Less frequently reported (less than 1%) were elevations of alkaline phosphatase and bilirubin

*RENAL* – elevations of the BUN (1 2%) Less frequently reported (less than 1%) were elevations of creatinine and the presence of casts in the urine

*CENTRAL NERVOUS SYSTEM* – headache or dizziness were reported occasionally (less than 1%)

*GENITOURINARY* – moniliasis or vaginitis were reported occasionally (less than 1%)

*MISCELLANEOUS* – diaphoresis and flushing were reported occasionally (less than 1%)

Other rarely observed adverse reactions (less than 0 1%) include leukocytosis, lymphocytosis, monocytosis, basophilia, a decrease in the prothrombin time, jaundice, glycosuria, hematuria, bronchospasm, serum sickness, abdominal pain, colitis, flatulence, dyspepsia, palpitations and epistaxis

**DOSAGE AND ADMINISTRATION:** Rocephin may be administered intravenously or intramuscularly The usual adult daily dose is 1 to 2 gm given once a day (or in equally divided doses twice a day) depending on the type and severity of the infection The total daily dose should not exceed 4 grams

For the treatment of serious miscellaneous infections in children, other than meningitis, the recommended total daily dose is 50 to 75 mg/kg (not to exceed 2 grams), given in divided doses every 12 hours

Generally, Rocephin therapy should be continued for at least two days after the signs and symptoms of infection have disappeared The usual duration is 4 to 14 days, in complicated infections longer therapy may be required

In the treatment of meningitis, a daily dose of 100 mg/kg (not to exceed 4 grams), given in divided doses every 12 hours, should be administered with or without a loading dose of 75 mg/kg

For the treatment of uncomplicated gonococcal infections, a single intramuscular dose of 250 mg is recommended

For preoperative use (surgical prophylaxis), a single dose of 1 gm administered ½ to 2 hours before surgery is recommended

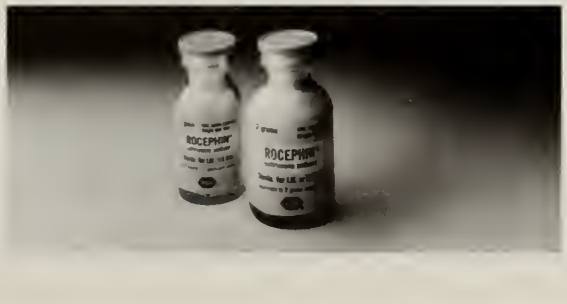
When treating infections caused by *Streptococcus pyogenes*, therapy should be continued for at least ten days

No dosage adjustment is necessary for patients with impairment of renal or hepatic function however, blood levels should be monitored in patients with severe renal impairment (e g , dialysis patients) and in patients with both renal and hepatic dysfunctions

**HOW SUPPLIED:** Rocephin (ceftriaxone sodium/Roche) is supplied as a sterile crystalline powder in glass vials and piggyback bottles The following packages are available

Vials containing 250 mg equivalent of ceftriaxone Boxes of 10 (NDC 0004 1962 01)
Vials containing 500 mg equivalent of ceftriaxone Boxes of 10 (NDC 0004 1963 01)
Vials containing 1 gm equivalent of ceftriaxone Boxes of 10 (NDC 0004 1964 01)
Piggyback bottles containing 1 gm equivalent of ceftriaxone Boxes of 10 (NDC 0004 1964 03)
Vials containing 2 gm equivalent of ceftriaxone Boxes of 10 (NDC 0004 1965 01)
Piggyback bottles containing 2 gm equivalent of ceftriaxone Boxes of 10 (NDC 0004 1965 03)
Bulk pharmacy containers, containing 10 gm equivalent of ceftriaxone Boxes of 1 (NDC 0004 1971 01)
NOT FOR DIRECT ADMINISTRATION

Roche Laboratories
Division of Hoffmann-La Roche Inc.
Nutley, New Jersey 07110




**References:**

1. Data on file, Hoffmann-La Roche Inc.
2. Patel IH, Kaplan SA: *Am J Med* 77:17-25, Oct 19, 1984
3. Richards DM, *et al*: *Drugs* 27:469-527, 1984.
4. Cleeland R, Squires E: *Am J Med* 77:3-11, Oct 19, 1984
5. Tanner DJ, Nazarian MQ: *Am J Med* 77:104-111, Oct 19, 1984

# Mean,

Powerful against susceptible pathogens.*

# lean &

Easy on tight budgets.

# clean.

Gentle to patients (generally well tolerated).

The one antimicrobial that
belongs on every formulary.

## Once-a-day

# Rocephin® ROCHE IV·IM

## ceftriaxone sodium/Roche

* ROCEPHIN is indicated in the following infections: bacterial septicemia, bone and joint, intra-abdominal, lower respiratory tract, skin and skin structure, urinary tract, bacterial meningitis and gonorrhea. Please see summary of product information on adjacent page for indicated susceptible organisms.

Copyright © 1987 by Hoffmann-La Roche Inc. All rights reserved.

Please see adjacent page for summary of product information.

THE FRANCIS A. COUNTWAY
LIBRARY OF MEDICINE
BOSTON, MA

SEP 30 1987

INCORPORATING
ARIZONA MEDICINE

SEE PAGE 570

DISPLAY
SHELVES

# The Western Journal of Medicine

VOLUME 146 • NUMBER 5 MAY 1987

**CLINICAL INVESTIGATION**

571 Serum Potassium Concentration in Hyperglycemia of Diabetes Mellitus With Long-term Dialysis
A H TZAMALOUKAS and P S AVASTHI

**CLINICAL MEDICINE**

576 Use of Intravenous Pyelography in Blunt Trauma—A Reappraisal
J R HOFFMAN, R R SIMON, M SMITH, G STROM and L J BARAFF

580 A Practical Approach to Improving Pain Control in Cancer Patients
M L BRIGDEN and J B BARNETT

**MEDICAL PROGRESS**

585 Hypoglycemic Syndrome in Infancy and Childhood—A Surgeon's Perspective
A R MOOSA, L BAKER and M LAVELLE-JONES

**CLINICOPATHOLOGIC CONFERENCE**

589 Multiple Cerebral Emboli in a Young Man
M P NESPECA and J J TOWNSEND

596 Editorial Comment: Stroke in Young People—The Heart of the Matter
R G HART and G L FREEMAN

**MEDICAL STAFF CONFERENCE**

598 Acute Pancreatitis
Discussants: J H GRENDELL and J EGAN

**EPITOMES**

603 Important Advances in Emergency Medicine

**EDITORIALS**

612 Whatever Happened to Report MM? • The Surgeon's Approach to Hypoglycemia in Infants and Children • Primary Care—Does It Have a Future?

**CASE REPORTS**

614 The Corticotropin-Releasing Factor Test in the Diagnosis of Ectopic ACTH Secretion
E CAGLIERO and M LORENZI

615 Acquired Immunodeficiency Syndrome Presenting as Schizophrenia
M A CUMMINGS, K L CUMMINGS, M H RAPAPORT, J H ATKINSON and I GRANT

618 A 32-Year-Old Man With the Acquired Immunodeficiency Syndrome and Pneumococcal Meningitis
D V HAVLIR, M D WITT and M SANDE

**CORRESPONDENCE**

620 Alcohol and Other Drug Dependence Among Latinos • Donor Notification for Positive Non-A, Non-B Hepatitis Surrogate Testing • The Achilles Heel of Computer-Initiated Bibliographic Search • Dietary Cholesterol and Atherosclerosis • The Role of Irradiation • Incidence of Cough Associated With Captopril Therapy

**TOPICS IN PRIMARY CARE MEDICINE**

623 Urinary Incontinence
K KROENKE and G D CORRIE

**HEALTH CARE DELIVERY**

627 Survival Following Cardiac Transplantation—What Are Acceptable Standards?
D G RENLUND, M R BRISTOW, N A BURTON, K W JONES, S V KARWANDE and W A GAY, Jr

**PUBLIC HEALTH AND PREVENTIVE MEDICINE**

631 Preventive Dentistry Update—Dental Sealants
R ISMAN and K W KIZER

**MEDICAL ETHICS**

633 Consultations in Clinical Ethics—Issues and Questions in 27 Cases
J LA PUMA

**INFORMED OPINION**

638 Physicians and the Death Penalty
K M THORBURN

**OTHER FEATURES**

552 Books Received

558 Subscription Information

560 Continuing Medical Education Activities in Arizona; California, Hawaii and Nevada; Idaho; Montana; New Mexico; Utah; Washington; Wyoming

643 Idaho Medical Association Annual Meeting

647 Classified Advertising

653 Arizona Medical Association Annual Meeting

655 Wyoming Medical Society Annual Meeting

657 Western State Medical Associations' Meetings

**Detailed Table of Contents:** 547, 550, 564

Official Journal of the Arizona Medical Association, the California Medical Association, the Idaho Medical Association, the Montana Medical Association, the Nevada State Medical Association, the New Mexico Medical Society, the Utah State Medical Association, the Washington State Medical Association and the Wyoming Medical Society. Affiliated Specialty Society: California Society of Internal Medicine.

Affiliated Clinical Investigation Societies: the Western Association of Physicians; the Western Society for Clinical Investigation; the Western Section, American Federation for Clinical Research; the Western Society for Pediatric Research; the Western Region, Society for Investigative Dermatology.

# A million and 1

## A poetic understatement

The actual number is in the billions. For more than 15 years, Dalmane (flurazepam HCl/Roche) has been providing sleep that satisfies patients—sleep that comes quickly and lasts through the night.[1-8]

Sleep that satisfies *you*—you can count on an exceptionally wide margin of safety.[7-9] As always, caution patients about driving or drinking alcohol.

ROCHE®

Copyright © 1986 by Roche Products Inc All rights reserved

# nights of sleep...

# DALMANE®

brand of
flurazepam HCl/Roche Ⓥ

## sleep that satisfies

Please see adjacent page for references and summary of product information

**References:** 1. Kales J, *et al: Clin Pharmacol Ther 12* 691-697, Jul-Aug 1971 2. Kales A, *et al: Clin Pharmacol Ther 18*.356-363, Sep 1975. 3. Kales A, *et al. Clin Pharmacol Ther 19* 576-583, May 1976. 4. Kales A, *et al. Clin Pharmacol Ther 32*:781-788, Dec 1982 5. Frost JD Jr, DeLucchi MR: *J Am Geriatr Soc 27*.541-546, Dec 1979 6. Dement WC, *et al: Behav Med*, pp. 25-31, Oct 1978 7. Kales A, Kales JD: *J Clin Psychopharmacol 3*.140-150, Apr 1983 8. Tennant FS, *et al*. Symposium on the Treatment of Sleep Disorders, Telecanference, Oct 16, 1984 9. Greenblatt DJ, Allen MD, Shader RI: *Clin Pharmacol Ther 21*.355-361, Mar 1977.

**DALMANE®**
brand of
flurazepam HCl/Roche ®
**sleep that satisfies**
15-mg/30-mg capsules

**Before prescribing, please consult complete product information, a summary of which follows:**
**Indications:** Effective in all types of insomnia characterized by difficulty in falling asleep, frequent nocturnal awakenings and/or early morning awakening, in patients with recurring insomnia or poor sleeping habits, in acute or chronic medical situations requiring restful sleep. Objective sleep laboratory data have shown effectiveness for at least 28 consecutive nights of administration. Since insomnia is often transient and intermittent, prolonged administration is generally not necessary or recommended. Repeated therapy should only be undertaken with appropriate patient evaluation.
**Contraindications:** Known hypersensitivity to flurazepam HCl, pregnancy. Benzodiazepines may cause fetal damage when administered during pregnancy. Several studies suggest an increased risk of congenital malformations associated with benzodiazepine use during the first trimester. Warn patients of the potential risks to the fetus should the possibility of becoming pregnant exist while receiving flurazepam. Instruct patients to discontinue drug prior to becoming pregnant. Consider the possibility of pregnancy prior to instituting therapy.
**Warnings:** Caution patients about possible combined effects with alcohol and other CNS depressants. An additive effect may occur if alcohol is consumed the day following use for nighttime sedation. This potential may exist for several days following discontinuation. Caution against hazardous occupations requiring complete mental alertness (*e.g.*, operating machinery, driving). Potential impairment of performance of such activities may occur the day following ingestion. Not recommended for use in persons under 15 years of age. Withdrawal symptoms rarely reported; abrupt discontinuation should be avoided with gradual tapering of dosage for those patients on medication for a prolonged period of time. Use caution in administering to addiction-prone individuals or those who might increase dosage.
**Precautions:** In elderly and debilitated patients, it is recommended that the dosage be limited to 15 mg to reduce risk of oversedation, dizziness, confusion and/or ataxia. Consider potential additive effects with other hypnotics or CNS depressants. Employ usual precautions in severely depressed patients, or in those with latent depression or suicidal tendencies, or in those with impaired renal or hepatic function.
**Adverse Reactions:** Dizziness, drowsiness, lightheadedness, staggering, ataxia and falling have occurred, particularly in elderly or debilitated patients. Severe sedation, lethargy, disorientation and coma, probably indicative of drug intolerance or overdosage, have been reported. Also reported: headache, heartburn, upset stomach, nausea, vomiting, diarrhea, constipation, GI pain, nervousness, talkativeness, apprehension, irritability, weakness, palpitations, chest pains, body and joint pains and GU complaints. There have also been rare occurrences of leukopenia, granulocytopenia, sweating, flushes, difficulty in focusing, blurred vision, burning eyes, faintness, hypotension, shortness of breath, pruritus, skin rash, dry mouth, bitter taste, excessive salivation, anorexia, euphoria, depression, slurred speech, confusion, restlessness, hallucinations, and elevated SGOT, SGPT, total and direct bilirubins, and alkaline phosphatase, and paradoxical reactions, *e.g.*, excitement, stimulation and hyperactivity.
**Dosage:** Individualize for maximum beneficial effect. *Adults*: 30 mg usual dosage, 15 mg may suffice in some patients. *Elderly or debilitated patients*: 15 mg recommended initially until response is determined.
**Supplied:** Capsules containing 15 mg or 30 mg flurazepam HCl.

ROCHE®
Roche Products Inc
Manati, Puerto Rico 00701

***The Western Journal of Medicine***
(ISSN 0093-0415/USPS 084 480) is published monthly for $30 per year (USA and Canada) by the California Medical Association, 44 Gough Street, San Francisco, CA 94103. Second-class postage paid at San Francisco, CA and additional mailing offices.
**POSTMASTER:** Send address changes to *The Western Journal of Medicine*, Circulation, P.O. Box 7602, San Francisco, CA 94120-7602.

# *Moving?*

Please give us six weeks notice and supply your personal reference number.

ID No.

The Western Journal of Medicine
P.O. Box 7602
San Francisco, CA 94120-7602.

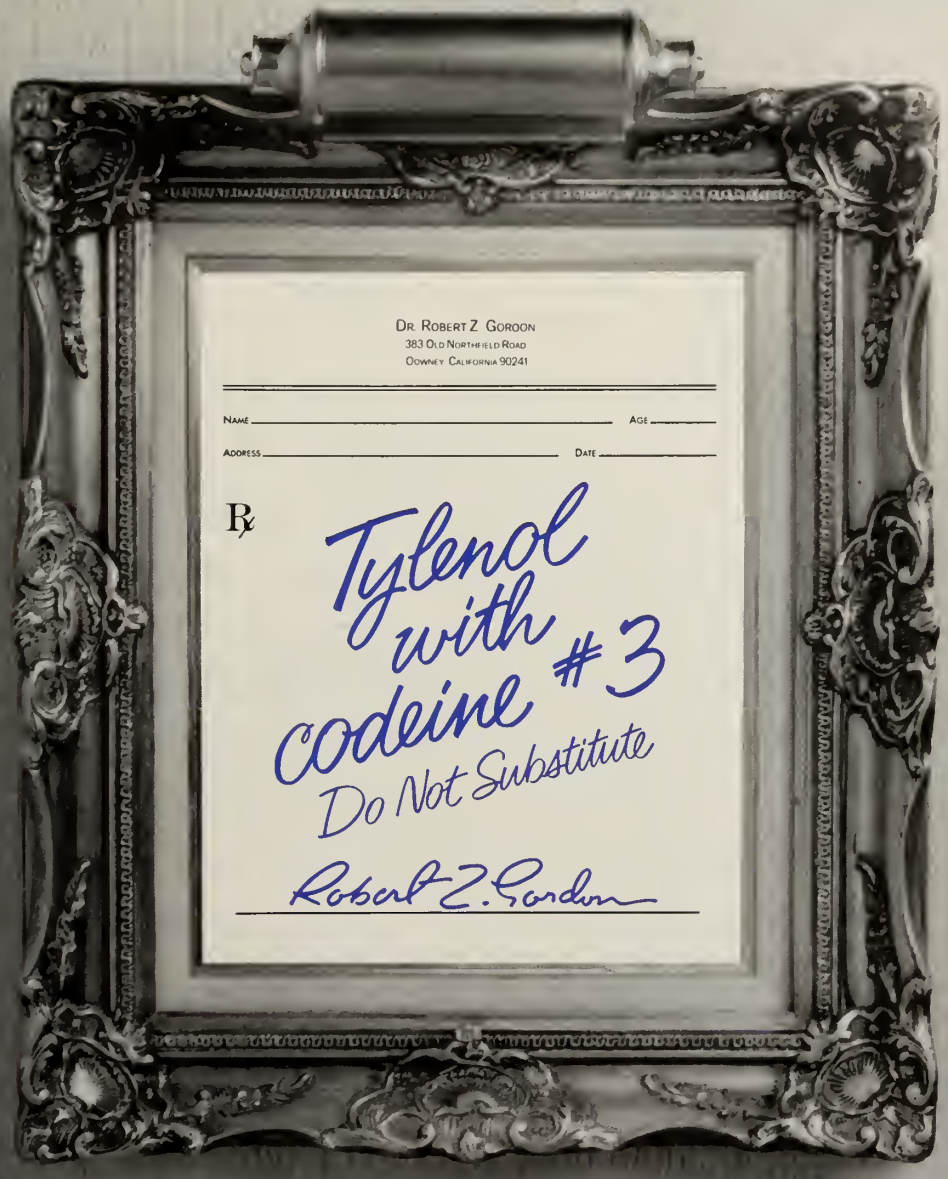
302703 XX

**The Western Journal of Medicine**
P.O. Box 7602, San Francisco, CA 94120-7602

**This Publication is available in Microform.**

**University Microfilms International**

Please send additional information
for _____ (name of publication)
Name_____
Institution_____
Street_____
City_____
State_____ Zip_____
300 North Zeeb Road, Dept. P.R., Ann Arbor, Mi. 48106




# CREATE A SIGNED ORIGINAL

## to be sure your patients get...

# Tylenol®

ACETAMINOPHEN

**with codeine phosphate**

TABLETS C III ELIXIR C V

**Tablets:** Contain Codeine Phosphate*: No. 3 — 30 mg; No. 4 — 60 mg — plus Acetaminophen 300 mg.

**Elixir:** Each 5 mL contains 12 mg Codeine Phosphate* plus 120 mg Acetaminophen (Alcohol 7%).

*Warning: May be habit forming.

© McNEILAB, INC., 1987

TYCT 6445-A

# When considering professional liability protection, choose the Mutual Protection Trust

| Specialty | 1987 CAP/MPT Estimated Cost* |
|---|---|
| Allergy | $ 2,371 |
| Anesthesia | 15,840 |
| Cardiology with invasive vascular procedures | 10,924 |
| Cardiology — no invasive vascular procedures | 5,222 |
| Dermatology — no radiation or hair transplants | 5,222 |
| Gastroenterology with endoscopy and ERCP, board certified | 8,073 |
| Family Practice — no surgery | 5,222 |
| Family Practice — minor surgery or assisting at surgery | 8,073 |
| Family Practice — major surgery | 17,905 |
| General Surgery | 17,905 |
| Internal Medicine with invasive vascular procedures | 10,924 |
| Internal Medicine — no invasive vascular procedures | 5,222 |
| Neurology — no electro-convulsive therapy | 2,371 |
| Ophthalmology with surgery or laser | 8,073 |
| Orthopedics with spinal surgery | 22,035 |
| Orthopedics — no spinal surgery | 19,970 |
| Otolaryngology — doing plastic surgery, board certified | 17,905 |
| Pediatrics — General | 2,371 |
| Pediatrics — General, with invasive vascular procedures | 10,924 |
| Plastic Surgery, board certified | 17,905 |
| Psychiatry — no electro-convulsive therapy | 2,371 |
| Radiology — diagnostic, no coronary angiography | 5,222 |
| Radiology — including coronary angiography | 10,924 |
| Urology | 13,775 |

*These rates include dues and assessments for a CAP/MPT member with 50 or more months of membership or retroactive coverage (matured rate). CAP/MPT offers coverage limits of $1 million per occurrence with an aggregate of $3 million per year.

**CAP/MPT offers:**

- **EXPERIENCE: The oldest California Trust providing professional liability protection**
- QUALITY: Stringent screening process — each member has a voice in the selection of new members
- **SAVINGS: Compare our cost with other experienced providers of malpractice protection**
- REINSURANCE: Limits assessment exposure
- **LOSS PREVENTION PROGRAMS: Education reduces malpractice risk**
- RETROACTIVE COVERAGE: For qualified members

In addition to dues and assessments, CAP/MPT members pay a one-time initial trust contribution based on risk classification. This can be paid in installments and is refundable under the terms of the MPT Agreement.

**MUTUAL PROTECTION TRUST**

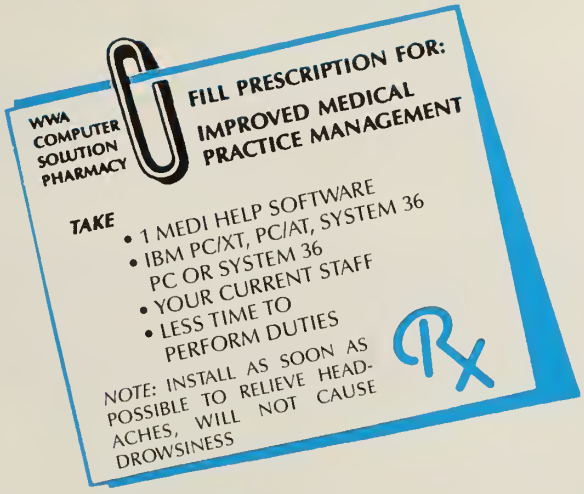
**Cooperative of American Physicians, Inc.**

P.O. Box 76998
Los Angeles, CA 90076-0998

**(800) 252-7706**

Call to find out what your cost would be with MPT

# JUST WHAT THE DOCTOR ORDERED




## MEDI HELP AND IBM FOR THE MEDICAL ENVIRONMENT

### FLEXIBILITY

* MEDI HELP will accommodate multiple locations.
* MEDI HELP will handle multiple doctors.
* MEDI HELP will track up to fifteen financial categories with six categories per patient and four insurance carriers per category.
* MEDI HELP will provide insurance billings.
* MEDI HELP will grow with your practice and data can transfer to a larger computer without a conversion.

### CONTROLS

* MEDI HELP will accommodate many terminals and printers, A TRUE MULTI-USER, MULTI-TASKING SYSTEM.
* MEDI HELP provides multi-level security for your practice.
* MEDI HELP provides adjustment reports by operator and choices for posting payments.

### OUR SERVICES BEGIN WITH YOUR PHONE CALL

* * * Consultation and Needs Analysis
* * * Demonstration at Your Location or Ours
* * * System Installation and Operation Training
* * * Thirty (30) Day Software Trial Period
* * * Local Support in Some Areas
* * * Telephone Support
* * * Periodic Revisions/Enhancements to Software
* * * Assistance with Data Conversion Available
* * * Software Customizing Available

### TIME SAVINGS

* MEDI HELP provides addition of new codes for files without terminating the current task.
* MEDI HELP provides HELP KEY SUPPORT.
* MEDI HELP provides default values to reduce keying.
* MEDI HELP provides electronic claims processing.

### EFFICIENCY

* MEDI HELP will locate the patient within files by name search.
* MEDI HELP allows front office super-bills and/or back office operation.
* MEDI HELP provides patient recall notices.

WILLIAMS, WRIGHT & ASSOCIATES, INC.

SINCE 1977

CORPORATE OFFICES
400 N. Mountain Avenue, Suite 305
Upland, California 91786
**(714) 985-0809**
**1 (800) 345-3634**

Branch offices located in San Francisco, California and Kennewick, Washington.

MEDICAL PRACTICE MANAGEMENT SYSTEM

NAME:_____ PRACTICE NAME:_____

ADDRESS:_____

CITY:_____ STATE:_____ ZIP:_____

PHONE:_____

MAIL THIS FORM TODAY FOR A HANDS-ON DEMONSTRATION OR A NO COST OR OBLIGATION CONSULTATION.

*An IBM Marketing Assistance Program Participant.* **IBM is a registered trade mark of International Business Machines*

For California, Idaho, Montana, Oregon and Washington doctors only.

THE FRANCIS A. COUNTWAY
LIBRARY OF MEDICINE
BOSTON, MA
SEP 30 1987

SINCE 1902

# The Western Journal of Medicine

ISSN 0093-0415

PO BOX 7602 • SAN FRANCISCO, CALIFORNIA 94120-7602 • TELEPHONE (415) 863-5522

MALCOLM S. M. WATTS, MD, *Editor*
LLOYD H. SMITH, Jr, MD, *Associate Editor*
DAVID GREER, *Managing Editor*

SALLY LINEBARGER, *Assistant Managing Editor*
SANDRA WILLETT, *Editorial Assistant*

JANICE ANDERSEN, *Copy Editor*
TERESA A. MORRISSEY, *Advertising Production Manager*
FRITZ C. HEATON, *Circulation Coordinator*

editorial communications to DR WATTS • business communications to MR GREER

Official Journal of the Arizona Medical Association, the California Medical Association, the Idaho Medical Association, the Montana Medical Association, the Nevada State Medical Association, the New Mexico Medical Society, the Utah State Medical Association, the Washington State Medical Association and the Wyoming Medical Society.

Affiliated Clinical Investigation Societies: the Western Association of Physicians; the Western Society for Clinical Investigation; the Western Section, American Federation for Clinical Research; the Western Society for Pediatric Research; the Western Region, Society for Investigative Dermatology.

Affiliated Specialty Society: California Society of Internal Medicine.

## EDITORIAL BOARD

*Chairman of the Board*
Malcolm S. M. Watts, San Francisco, Calif

*Associate Editor*
Lloyd H. Smith, Jr, San Francisco, Calif

*Editor for Clinical Investigation*
Kenneth D. Gardner, Jr, Albuquerque, NM

*Special Editor for Arizona*
Marshall B. Block, Phoenix, Ariz

*Special Editor for Idaho*
E. R. W. Fox, Coeur d'Alene, Idaho

*Special Editor for Montana*
Michael R. Oreskovich, Kalispell, Mont

*Special Editor for Nevada*
Owen C. Peck, Reno, Nev

*Special Editor for New Mexico*
I. Brian Taylor, Carlsbad, NM

*Special Editor for Utah*
John H. Holbrook, Salt Lake City, Utah

*Special Editor for Washington*
David Hopkins, Federal Way, Wash

*Special Editor for Wyoming*
Joseph P. Murphy, Casper, Wyo

*Allergy*
Harold S. Novey, Orange, Calif
Merle S. Scherr, Scottsdale, Ariz

*Anesthesiology*
Ronald D. Miller, San Francisco, Calif

*Cardiac and Thoracic Surgery*
Norman E. Shumway, Stanford, Calif

*Chest Diseases*
Leonard D. Hudson, Seattle, Wash
Thomas L. Petty, Denver, Colo

*Dermatology*
John H. Epstein, San Francisco, Calif
Clark Huff, Denver, Colo
Frank Parker, Portland, Ore
Gerald D. Weinstein, Irvine, Calif

*Emergency Medicine*
William A. Boehm, Alamogordo, NM
W. Richard Bukata, Van Nuys, Calif
Clark Chipman, Portland, Ore
Thomas Elmendorf, Davis, Calif

*General and Family Practice*
Harmon E. Holverson, Emmett, Idaho
Charles W. Huff, Casper, Wyo
Daniel D. Roberts, Central Point, Ore
J. Jerome Wildgen, Kalispell, Mont

*Internal Medicine*
Philip R. Alper, Burlingame, Calif
Robert W. Burroughs, Spokane, Wash
Theodore C. Eickhoff, Denver, Colo
Robert L. Hare, Portland, Ore
Harry R. Kimball, Boston, Mass
Robert H. Moser, Skokie, Ill
George A. Porter, Portland, Ore
Helen M. Ranney, San Diego, Calif
Laurens P. White, San Francisco, Calif
Ralph C. Williams, Jr, Albuquerque, NM

*Neurology*
J. Richard Baringer, Salt Lake City, Utah
Don F. Seelinger, Albuquerque, NM
W. C. Wiederholt, La Jolla, Calif

*Neurosurgery*
John R. Green, Phoenix, Ariz
George A. Ojemann, Seattle, Wash
Charles B. Wilson, San Francisco, Calif

*Nuclear Medicine*
Joseph P. Kriss, Stanford, Calif

*Obstetrics and Gynecology*
Ralph W. Hale, Honolulu, Hawaii
W. LeRoy Heinrichs, Stanford, Calif
Morton A. Stenchever, Seattle, Wash

*Occupational Medicine*
Linda Hawes Clever, San Francisco, Calif

*Ophthalmology*
John L. Keltner, Davis, Calif
Bruce E. Spivey, San Francisco, Calif

*Orthopedics*
Ernest M. Burgess, Seattle, Wash
George E. Omer, Albuquerque, NM

*Otolaryngology*
Roger Boles, San Francisco, Calif
Paul H. Ward, Los Angeles, Calif

*Pathology*
Roy I. Davis, Phoenix, Ariz

*Pediatrics*
Allen W. Mathies, Jr, Pasadena, Calif
William O. Robertson, Seattle, Wash
Arnold L. Smith, Seattle, Wash

*Pharmacology*
Rubin Bressler, Tucson, Ariz

*Physical Medicine and Rehabilitation*
Robert G. Taylor, Sacramento, Calif

*Plastic Surgery*
Richard P. Jobe, Los Altos, Calif
Henry K. Kawamoto, Jr, Santa Monica, Calif

*Preventive Medicine and Public Health*
Joseph L. Lyon, Salt Lake City, Utah
Jonathan Mann, Geneva, Switz

*Psychiatry*
Ralph Crawshaw, Portland, Ore
Alan I. Levenson, Tucson, Ariz
R. Bruce Sloane, Los Angeles, Calif
Joe Paul Tupin, Sacramento, Calif

*Radiology*
M. Paul Capp, Tucson, Ariz
Albert A. Moss, Seattle, Wash
Marshall Rowen, Orange, Calif

*Surgery*
John Wesley Batdorf, Las Vegas, Nev
Daniel T. Cloud, Phoenix, Ariz
Paul A. Ebert, Chicago, Ill
Frank G. Moody, Houston, Tex

*Urology*
Richard Middleton, Salt Lake City, Utah
Thomas A. Stamey, Stanford, Calif

*Senior Members at Large*
Louis K. Diamond, San Francisco, Calif
Edgar Wayburn, San Francisco, Calif

## ADVISORY BOARD, CLINICAL INVESTIGATION

George D. Molnar, Univ of Alberta
Murray A. Katz, Univ of Arizona
Ross E. Petty, Univ of British Columbia
Eldon Shaffer, Univ of Calgary
M. Eric Gershwin, Univ of California, Davis
Jacob Katz, Univ of California, Irvine
Delbert A. Fisher, Univ of California, Los Angeles
Kenneth M. Moser, Univ of California, San Diego
H. Benfer Kaltreider, Univ of California, San Francisco
Alan S. Nies, Univ of Colorado
Irwin J. Schatz, Univ of Hawaii
John Peacock, Univ of Nevada
Sanford Schneider, Loma Linda Univ
Kenneth D. Gardner, Jr, Univ of New Mexico
J. David Bristow, Univ of Oregon
Robert M. McAllister, Univ of Southern California
R. Marvin Bala, Univ of Saskatchewan
Allen D. Cooper, Stanford Univ
Gerald Rothstein, Univ of Utah
David R. Saunders, Univ of Washington

## ADVERTISING INFORMATION

Advertising Sales Representatives

EAST: Saul G. Hornik, SGH, Inc, 12 Court Street, Freehold, NJ 07728 • (201) 972-1911/462-7422
MIDWEST: SGH, Inc, 100 South Wacker Drive, Suite 2030, Chicago, IL 60606 • (312) 782-1100
WEST: Lynne Jeffes, 1340 Paloma Avenue, Burlingame, CA 94010 • (415) 348-7478
CLASSIFIED: PO Box 7602, San Francisco, CA 94120-7602 • Tel: (415) 863-5522/863-6853

*Advertisements*—The journal is published the first week of the month. Advertising copy must be received no later than the first of the month preceding issue. Advertising rates will be sent on request. Acceptance of advertising is contingent upon approval by the Advertising Committee. *The journal reserves the right to reject any advertisement.*

## SUBSCRIPTION INFORMATION

The subscription price per year is $30 in the United States and Canada (US funds); $50 in all other countries. Single copies are $4.50 (which includes postage and handling). Address all subscription communications to:
THE WESTERN JOURNAL OF MEDICINE Circulation, PO Box 7602
San Francisco, CA 94120-7602 • Tel: (415) 863-5522, Ext 245

Allow six weeks for subscriptions to begin. Past issues must be bought individually. So long as reserve stocks are available, missing issue requests from subscribers are honored for up to six months after the issue date. Thereafter, the single copy rate of $4.50 is applicable for each issue available.

*Change of Address*—Requests for change of address should give both the old and new address. Allow six weeks for changeover.

## SUBMITTING MANUSCRIPTS

Manuscripts for consideration should be sent to the editor, Malcolm S. M. Watts, MD, PO Box 7602, San Francisco, CA 94120-7602.

*"Information for Authors"*—A complete guide to manuscript submission and *WJM* style appears in the January and July issues. Manuscripts may be prepared in accordance with the "Uniform Requirements for Manuscripts Submitted to Biomedical Journals" (*British Medical Journal*, June 12, 1982; *Annals of Internal Medicine*, June 1982).

*Author Responsibility*—Authors are responsible for all statements, conclusions and methods of presenting subjects. Articles are accepted on condition that they are contributed solely to this journal.

*Manuscripts*—Ordinarily manuscripts should not exceed 3,000 words (less than 15 typed double-spaced pages). The *original* manuscript and two copies should be submitted, typed double-spaced throughout. If photographic illustrations are desired, three sets of clear, unmounted black and white glossy prints should be supplied. For line drawings, original artwork or glossy prints are acceptable. Tables should be typed on separate sheets of paper.

*Clinical Investigation*—Papers that authors wish considered for the Clinical Investigation section should be so designated in the transmittal letter. Such papers should describe experimental work in humans that extensively and prospectively examines scientific hypotheses relating to disease.

## PUBLISHER

Copyright 1987 by the California Medical Association • Owned and Published by the California Medical Association.

All material subject to this copyright appearing in THE WESTERN JOURNAL OF MEDICINE may be photocopied for the noncommercial purpose of scientific or educational advancement. Volumes begin with January and July.

POLICY COMMITTEE
Frederick S. Armstrong
Laurens P. White
Richard F. Corlin
Charles W. Plows
Howard L. Lang
Roger K. Howe
Malcolm S. M. Watts

Second class postage paid at San Francisco and at additional mailing offices (USPS 084 480).

# ANNOUNCING AUDIO-DIGEST

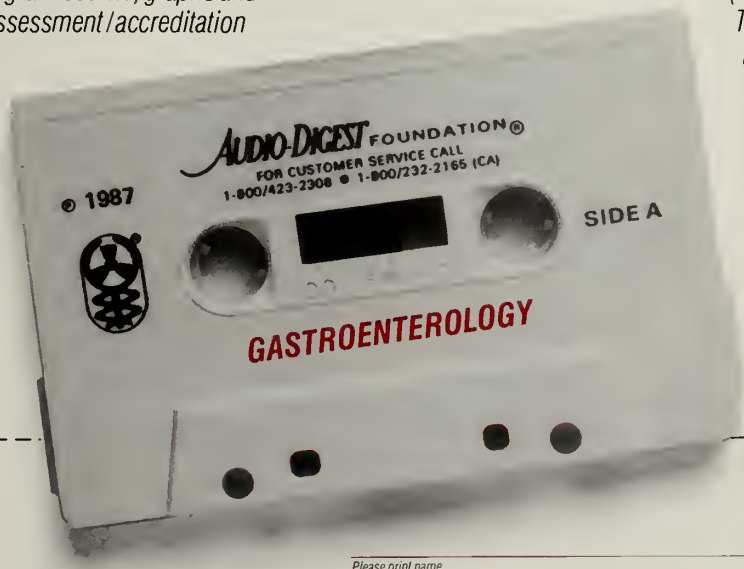
*Totally Integrated Medical Education*

## GASTROENTEROLOGY

***Audio-Digest is pleased to announce its newest "Spoken Medical Journal" subscription service.***

***As a charter member you receive:***

- ***CURRENT CLINICAL INFORMATION.*** *Updates, in-depth reviews, and all the latest Gastroenterology information on current developments months ahead of printed publication.*
- ***EDITORIAL EXCELLENCE.*** *Each program is meticulously edited from recordings of meetings and symposia, in all parts of the world, presenting smooth, clear and concise delivery of clinical information.*
- ***ACCOMPANYING PRINTED MATERIALS.*** *Each program includes printed program outline, graphs and charts, references and self-assessment/accreditation examination.*
- ***CATEGORY I APPROVED.*** *Each one-hour program is eligible for two Category I credit hours toward the American Medical Association's Physician's Recognition Award —at no added charge.*
- ***CASSETTE REFERENCE LIBRARY.*** *One full hour program each month in labeled box, with printed syllabus, (plus an annual index useful in locating speaker, topic, or program).*
- ***TAX DEDUCTIBLE.*** *Audio-Digest qualifies as a tax deductible business expense.*
- ***LOW PRICED CHARTER SUBSCRIPTION.*** *Enter your subscription now, and assure yourself of not only receiving Volume I, Issue 1, but you'll also receive two months (two issues) FREE. That's 14 issues (14 months) for the price of 12, for ONLY $69.00—a $50.70 savings off the individual issue price.*




FOR 35 YEARS, THE WORLD'S LEADER IN CONTINUING MEDICAL EDUCATION

## ORDER CERTIFICATE

*YES! I want to become a charter subscriber to Audio-Digest GASTROENTEROLOGY. Please enter my beginning subscription (14 issues for the price of 12)—$69.00. I understand each program includes valuable reference materials and a self-assessment/accreditation test. Pay now and receive a FREE Audio-Digest notebook to house the printed reference materials.*

☐ *Enclosed is my check for $69.00, payable to Audio-Digest Foundation*
☐ *Please bill me for $69.00.*

*FOR FASTER SERVICE CALL: 1-800/423-2308, in California 1-800/232-2165*

*Please print name* _____

*Address* _____

*City* _____ *State* _____ *Zip* _____

( ) _____

*Telephone* *(In case we have a question about your subscription.)*

**Audio-Digest** Foundation®
*A Non-Profit Subsidiary of the California Medical Association*
*1577 East Chevy Chase Drive, Glendale, California 91206*

6663

## News from DISTA about a new dosage form of cephalexin

## ANNOUNCING NEW

# Keflet™ TABLETS

# cephalexin

## All the advantages of cephalexin in a convenient tablet form

- Backed by over 15 years of clinical experience
- Smaller tablet is specially shaped and coated for easier swallowing
- May enhance patient compliance, particularly among the elderly
- Tablet dosage form may be appreciated by patients of all ages

## NEW Keflet Tablets are available as:

250-mg Tablets

500-mg Tablets

Keflet is contraindicated in patients with known allergy to the cephalosporins and should be given cautiously to penicillin-sensitive patients.

© 1987, DISTA PRODUCTS COMPANY

**Brief Summary. Consult the package literature for prescribing information.**

**Indications and Usage:** Keflet™ Tablets (cephalexin, Dista) are indicated for the treatment of the following infections when caused by susceptible strains of the designated microorganisms:

Respiratory tract infections caused by *Streptococcus pneumoniae* and group A β-hemolylic streptococci (Penicillin is the usual drug of choice in the treatment and prevention of streptococcal infections, including the prophylaxis of rheumatic fever. Keflet is generally effective in the eradication of streptococci from the nasopharynx, however, substantial data establishing the efficacy of Keflet in the subsequent prevention of rheumatic fever are not available at present.)

Otitis media due to *S pneumoniae, Haemophilus influenzae,* staphylococci, streptococci, and *Neisseria catarrhalis*

Skin and skin-structure infections caused by staphylococci and/or streptococci

Bone infections caused by staphylococci and/or *Proteus mirabilis*

Genitourinary tract infections, including acute prostatitis, caused by *Escherichia coli, P mirabilis,* and *Klebsiella* sp.

*Note*—Culture and susceptibility tests should be initiated prior to and during therapy. Renal function studies should be performed when indicated.

**Contraindication:** Keflet is contraindicated in patients with known allergy to the cephalosporin group of antibiotics.

**Warnings:** BEFORE CEPHALEXIN THERAPY IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO CEPHALOSPORINS AND PENICILLIN. CEPHALOSPORIN C DERIVATIVES SHOULD BE GIVEN CAUTIOUSLY TO PENICILLIN-SENSITIVE PATIENTS.

SERIOUS ACUTE HYPERSENSITIVITY REACTIONS MAY REQUIRE EPINEPHRINE AND OTHER EMERGENCY MEASURES.

There is some clinical and laboratory evidence of partial cross-allergenicity of the penicillins and the cephalosporins. Patients have been reported to have had severe reactions (including anaphylaxis) to both drugs.

Any patient who has demonstrated some form of allergy, particularly to drugs, should receive antibiotics cautiously. No exception should be made with regard to Keflet.

Pseudomembranous colitis has been reported with virtually all broad-spectrum antibiotics (including macrolides, semisynthetic penicillins, and cephalosporins); therefore, it is important to consider its diagnosis in patients who develop diarrhea in association with the use of antibiotics. Such colitis may range in severity from mild to life-threatening.

Treatment with broad-spectrum antibiotics alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is one primary cause of antibiotic-associated colitis.

Mild cases of pseudomembranous colitis usually respond to drug discontinuance alone. In moderate to severe cases, management should include sigmoidoscopy, appropriate bacteriologic studies, and fluid, electrolyte, and protein supplementation. When the colitis does not improve after the drug has been discontinued, or when it is severe, oral vancomycin is the drug of choice for antibiotic-associated pseudomembranous colitis produced by *C difficile.* Other causes of colitis should be ruled out.

*Usage in Pregnancy*—Safety of this product for use during pregnancy has not been established.

**Precautions:** *General*—Patients should be followed carefully so that any side effects or unusual manifestations of drug idiosyncrasy may be detected. If an allergic reaction to Keflet occurs, the drug should be discontinued and the patient treated with the usual agents (eg, epinephrine or other pressor amines, antihistamines, or corticosteroids).

Prolonged use of Keflet may result in the overgrowth of nonsusceptible organisms. Careful observation of the patient is essential. If superinfection occurs during therapy, appropriate measures should be taken.

Positive direct Coombs' tests have been reported during treatment with the cephalosporin antibiotics. In hematologic studies or in transfusion cross-matching procedures when antiglobulin tests are performed on the minor side or in Coombs' testing of newborns whose mothers have received cephalosporin antibiotics before parturition, it should be recognized that a positive Coombs' test may be due to the drug.

Keflet should be administered with caution in the presence of markedly impaired renal function. Under such conditions, careful clinical observation and laboratory studies should be made because safe dosage may be lower than that usually recommended.

Indicated surgical procedures should be performed in conjunction with antibiotic therapy.

As a result of administration of Keflet, a false-positive reaction for glucose in the urine may occur. This has been observed with Benedict's and Fehling's solutions and also with Clinitest® tablets but not with Tes-Tape® (Glucose Enzymatic Test Strip, USP, Lilly).

Broad-spectrum antibiotics should be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis.

*Usage in Pregnancy—Pregnancy Category B*—The daily oral administration of cephalexin to rats in doses of 250 or 500 mg/kg prior to and during pregnancy, or to rats and mice during the period of organogenesis only, had no adverse effect on fertility, fetal viability, fetal weight, or litter size. Note that the safety of cephalexin during pregnancy in humans has not been established.

Cephalexin showed no enhanced toxicity in weanling and newborn rats as compared with adult animals. Nevertheless, because the studies in humans cannot rule out the possibility of harm, Keflet should be used during pregnancy only if clearly needed.

*Nursing Mothers*—The excretion of cephalexin in the milk increased up to 4 hours after a 500-mg dose; the drug reached a maximum level of 4 μg/mL, then decreased gradually, and had disappeared 8 hours after administration. Caution should be exercised when Keflet is administered to a nursing woman.

**Adverse Reactions:** *Gastrointestinal*—Symptoms of pseudomembranous colitis may appear either during or after antibiotic treatment. Nausea and vomiting have been reported rarely. The most frequent side effect has been diarrhea. It was very rarely severe enough to warrant cessation of therapy. Dyspepsia and abdominal pain have also occurred. As with some penicillins and some other cephalosporins, transient hepatitis and cholestatic jaundice have been reported rarely.

*Hypersensitivity*—Allergic reactions in the form of rash, urticaria, angioedema, and, rarely, erythema multiforme, Stevens-Johnson Syndrome, or toxic epidermal necrolysis have been observed. These reactions usually subsided upon discontinuation of the drug. Anaphylaxis has also been reported.

Other reactions have included genital and anal pruritus, genital moniliasis, vaginitis and vaginal discharge, dizziness, fatigue, and headache. Eosinophilia, neutropenia, thrombocytopenia, and slight elevations in SGOT and SGPT have been reported.

PV 2211 DPP [111786]

*Additional information available to the profession on request from*

DISTA

**Dista Products Company**
Division of Eli Lilly and Company
Indianapolis, Indiana 46285
Mfd by Eli Lilly Industries, Inc
Carolina, Puerto Rico 00630

720073

# 24-hour security for the hypertensive heart

## First-step cardiovascular protection

Reduces workload of the heart by reducing myocardial $O_2$ demand

Preserves $K^+$ balance

Normalizes stress-induced systolic peaks with cardioselective beta-one blockade

Contraindicated in sinus bradycardia, heart block greater than first degree, cardiogenic shock, and overt cardiac failure.

Please consult Brief Summary of Prescribing Information on the following page.

**Once-a-day in hypertension...**

**Lopressor®**
metoprolol tartrate

Changing the Course of Cardiovascular Care

**Geigy**

# First-step protection for the hypertensive heart

**Lopressor®**
**metoprolol tartrate USP**

**Tablets**
**Ampuls**
**Prefilled Syringes**

*BRIEF SUMMARY (FOR FULL PRESCRIBING INFORMATION, SEE PACKAGE INSERT)*

**CONTRAINDICATIONS**
**Hypertension and Angina**
Lopressor is contraindicated in sinus bradycardia, heart block greater than first degree, cardiogenic shock, and overt cardiac failure (see **WARNINGS**).
**Myocardial Infarction**
Lopressor is contraindicated in patients with a heart rate < 45 beats/min; second- and third-degree heart block; significant first-degree heart block (P-R interval ≥ 0 24 sec); systolic blood pressure < 100 mmHg, or moderate-to-severe cardiac failure (see **WARNINGS**).

**WARNINGS**
**Hypertension and Angina**
***Cardiac Failure:*** Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure, and beta blockade carries the potential hazard of further depressing myocardial contractility and precipitating more severe failure in hypertensive and angina patients who have congestive heart failure controlled by digitalis and diuretics, Lopressor should be administered cautiously Both digitalis and Lopressor slow AV conduction.

***In Patients Without a History of Cardiac Failure:*** Continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or given a diuretic. The response should be observed closely If cardiac failure continues, despite adequate digitalization and diuretic therapy, Lopressor should be withdrawn.

***Ischemic Heart Disease:*** Following abrupt cessation of therapy with certain beta-blocking agents, exacerbations of angina pectoris and, in some cases, myocardial infarction have occurred When discontinuing chronically administered Lopressor, particularly in patients with ischemic heart disease, the dosage should be gradually reduced over a period of 1-2 weeks and the patient should be carefully monitored. If angina markedly worsens or acute coronary insufficiency develops, Lopressor administration should be reinstated promptly, at least temporarily, and other measures appropriate for the management of unstable angina should be taken. Patients should be warned against interruption or discontinuation of therapy without the physician's advice Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue Lopressor therapy abruptly even in patients treated only for hypertension.

***Bronchospastic Diseases:*** **PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD, IN GENERAL, NOT RECEIVE BETA BLOCKERS. Because of its relative beta$_1$ selectivity, however, Lopressor may be used with caution in patients with bronchospastic disease who do not respond to, or cannot tolerate, other antihypertensive treatment. Since beta$_1$ selectivity is not absolute, a beta$_2$-stimulating agent should be administered concomitantly, and the lowest possible dose of Lopressor should be used. In these circumstances it would be prudent initially to administer Lopressor in smaller doses three times daily, instead of larger doses two times daily, to avoid the higher plasma levels associated with the longer dosing interval. (See DOSAGE AND ADMINISTRATION.)**

***Major Surgery:*** The necessity or desirability of withdrawing beta-blocking therapy prior to major surgery is controversial; the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures

Lopressor, like other beta blockers, is a competitive inhibitor of beta-receptor agonists, and its effects can be reversed by administration of such agents, e.g , dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension Difficulty in restarting and maintaining the heart beat has also been reported with beta blockers

***Diabetes and Hypoglycemia:*** Lopressor should be used with caution in diabetic patients if a beta-blocking agent is required Beta blockers may mask tachycardia occurring with hypoglycemia, but other manifestations such as dizziness and sweating may not be significantly affected

***Thyrotoxicosis:*** Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta blockade, which might precipitate a thyroid storm.

**Myocardial Infarction**
***Cardiac Failure:*** Sympathetic stimulation is a vital component supporting circulatory function, and beta blockade carries the potential hazard of depressing myocardial contractility and precipitating or exacerbating minimal cardiac failure.

During treatment with Lopressor, the hemodynamic status of the patient should be carefully monitored If heart failure occurs or persists despite appropriate treatment, Lopressor should be discontinued

***Bradycardia:*** Lopressor produces a decrease in sinus heart rate in most patients; this decrease is greatest among patients with high initial heart rates and least among patients with low initial heart rates Acute myocardial infarction (particularly inferior infarction) may in itself produce significant lowering of the sinus rate If the sinus rate decreases to < 40 beats/min, particularly if associated with evidence of lowered cardiac output, atropine (0 25-0 5 mg) should be administered intravenously If treatment with atropine is not successful, Lopressor should be discontinued, and cautious administration of isoproterenol or installation of a cardiac pacemaker should be considered

***AV Block:*** Lopressor slows AV conduction and may produce significant first- (P-R interval ≥0.26 sec), second-, or third-degree heart block. Acute myocardial infarction also produces heart block

If heart block occurs, Lopressor should be discontinued and atropine (0 25-0.5 mg) should be administered intravenously If treatment with atropine is not successful, cautious administration of isoproterenol or installation of a cardiac pacemaker should be considered.

***Hypotension:*** If hypotension (systolic blood pressure ≤ 90 mmHg) occurs, Lopressor should be discontinued, and the hemodynamic status of the patient and the extent of myocardial damage carefully assessed Invasive monitoring of central venous, pulmonary capillary wedge, and arterial pressures may be required. Appropriate therapy with fluids, positive inotropic agents, balloon counterpulsation, or other treatment modalities should be instituted. If hypotension is associated with sinus bradycardia or AV block, treatment should be directed at reversing these (see above).

***Bronchospastic Diseases:*** **PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD, IN GENERAL, NOT RECEIVE BETA BLOCKERS. Because of its relative beta$_1$ selectivity, Lopressor may be used with extreme caution in patients with bronchospastic disease. Because it is unknown to what extent beta$_2$-stimulating agents may exacerbate myocardial ischemia and the extent of infarction, these agents should *not* be used prophylactically. If bronchospasm not related to congestive heart failure occurs, Lopressor should be discontinued. A theophylline derivative or a beta$_2$ agonist may be administered cautiously, depending on the clinical condition of the patient. Both theophylline derivatives and beta$_2$ agonists may produce serious cardiac arrhythmias.**

**PRECAUTIONS**
**General**
Lopressor should be used with caution in patients with impaired hepatic function.
**Information for Patients**
Patients should be advised to take Lopressor regularly and continuously, as directed, with or immediately following meals. If a dose should be missed, the patient should take only the next scheduled dose (without doubling it). Patients should not discontinue Lopressor without consulting the physician.

Patients should be advised (1) to avoid operating automobiles and machinery or engaging in other tasks requiring alertness until the patient's response to therapy with Lopressor has been determined, (2) to contact the physician if any difficulty in breathing occurs; (3) to inform the physician or dentist before any type of surgery that he or she is taking Lopressor
**Laboratory Tests**
Clinical laboratory findings may include elevated levels of serum transaminase, alkaline phosphatase, and lactate dehydrogenase.
**Drug Interactions**
Catecholamine-depleting drugs (e g , reserpine) may have an additive effect when given with beta-blocking agents Patients treated with Lopressor plus a catecholamine depletor should therefore be closely observed for evidence of hypotension or marked bradycardia, which may produce vertigo, syncope, or postural hypotension.
**Carcinogenesis, Mutagenesis, Impairment of Fertility**
Long-term studies in animals have been conducted to evaluate carcinogenic potential. In 2-year studies in rats at three oral dosage levels of up to 800 mg/kg per day, there was no increase in the development of spontaneously occurring benign or malignant neoplasms of any type. The only histologic changes that appeared to be drug related were an increased incidence of generally mild focal accumulation of foamy macrophages in pulmonary alveoli and a slight increase in biliary hyperplasia Neither finding represents symptoms of a known disease entity in man. In a 21-month study in Swiss albino mice at three oral dosage levels of up to 750 mg/kg per day, benign lung tumors (small adenomas) occurred more frequently in female mice receiving the highest dose than in untreated control animals There was no increase in malignant or total (benign plus malignant) lung tumors, nor in the overall incidence of tumors or malignant tumors. This 21-month study was repeated in CD-1 mice, and no statistically or biologically significant differences were observed between treated and control mice of either sex for any type of tumor

All mutagenicity tests performed (a dominant lethal study in mice, chromosome studies in somatic cells, a Salmonella/mammalian-microsome mutagenicity test, and a nucleus anomaly test in somatic interphase nuclei) were negative

No evidence of impaired fertility due to Lopressor was observed in a study performed in rats at doses up to 55 5 times the maximum daily human dose of 450 mg
**Pregnancy Category C**
Lopressor has been shown to increase postimplantation loss and decrease neonatal survival in rats at doses up to 55 5 times the maximum daily human dose of 450 mg Distribution studies in mice confirm exposure of the fetus when Lopressor is administered to the pregnant animal. These studies have revealed no evidence of impaired fertility or teratogenicity There are no adequate and well-controlled studies in pregnant women Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed
**Nursing Mothers**
Lopressor is excreted in breast milk in very small quantity An infant consuming 1 liter of breast milk daily would receive a dose of less than 1 mg of the drug Caution should be exercised when Lopressor is administered to a nursing woman
**Pediatric Use**
Safety and effectiveness in children have not been established

**ADVERSE REACTIONS**
**Hypertension and Angina**
Most adverse effects have been mild and transient
***Central Nervous System:*** Tiredness and dizziness have occurred in about 10 of 100 patients Depression has been reported in about 5 of 100 patients Mental confusion and short-term memory loss have been reported Headache, nightmares, and insomnia have also been reported.
***Cardiovascular:*** Shortness of breath and bradycardia have occurred in approximately 3 of 100 patients Cold extremities, arterial insufficiency, usually of the Raynaud type; palpitations, congestive heart failure, peripheral edema; and hypotension have been reported in about 1 of 100 patients (See **CONTRAINDICATIONS, WARNINGS,** and **PRECAUTIONS** )
***Respiratory:*** Wheezing (bronchospasm) and dyspnea have been reported in about 1 of 100 patients (see **WARNINGS**).
***Gastrointestinal:*** Diarrhea has occurred in about 5 ot 100 patients Nausea, dry mouth, gastric pain, constipation, flatulence, and heartburn have been reported in about 1 of 100 patients.
***Hypersensitive Reactions:*** Pruritus or rash have occurred in about 5 ot 100 patients. Worsening of psoriasis has also been reported
***Miscellaneous:*** Peyronie's disease has been reported in fewer than 1 of 100,000 patients Musculoskeletal pain, blurred vision, and tinnitus have also been reported.

There have been rare reports of reversible alopecia, agranulocytosis, and dry eyes Discontinuation of the drug should be considered if any such reaction is not otherwise explicable.

The oculomucocutaneous syndrome associated with the beta blocker practolol has not been reported with Lopressor.
**Myocardial Infarction**
***Central Nervous System:*** Tiredness has been reported in about 1 of 100 patients. Vertigo, sleep disturbances, hallucinations, headache, dizziness, visual disturbances, confusion, and reduced libido have also been reported, but a drug relationship is not clear
***Cardiovascular:*** In the randomized comparison of Lopressor and placebo described in the **CLINICAL PHARMACOLOGY** section, the following adverse reactions were reported:

| | *Lopressor* | *Placebo* |
|---|---|---|
| Hypotension (systolic BP < 90 mmHg) | 27 4% | 23.2% |
| Bradycardia (heart rate < 40 beats/min) | 15 9% | 6.7% |
| Second- or third-degree heart block | 4 7% | 4.7% |
| First-degree heart block (P-R ≥ 0 26 sec) | 5 3% | 1.9% |
| Heart failure | 27.5% | 29 6% |

***Respiratory:*** Dyspnea of pulmonary origin has been reported in fewer than 1 of 100 patients.
***Gastrointestinal:*** Nausea and abdominal pain have been reported in fewer than 1 of 100 patients.
***Dermatologic:*** Rash and worsened psoriasis have been reported, but a drug relationship is not clear.
***Miscellaneous:*** Unstable diabetes and claudication have been reported, but a drug relationship is not clear.
**Potential Adverse Reactions**
A variety of adverse reactions not listed above have been reported with other beta-adrenergic blocking agents and should be considered potential adverse reactions to Lopressor.
***Central Nervous System:*** Reversible mental depression progressing to catatonia, an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics
***Cardiovascular:*** Intensification of AV block (see **CONTRAINDICATIONS**).
***Hematologic:*** Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura
***Hypersensitive Reactions:*** Fever combined with aching and sore throat, laryngospasm, and respiratory distress

**OVERDOSAGE**
**Acute Toxicity**
Several cases of overdosage have been reported, some leading to death

Oral $LD_{50}$'s (mg/kg): mice, 1158-2460, rats, 3090-4670.
**Signs and Symptoms**
Potential signs and symptoms associated with overdosage with Lopressor are bradycardia, hypotension, bronchospasm, and cardiac failure.
**Treatment**
There is no specific antidote

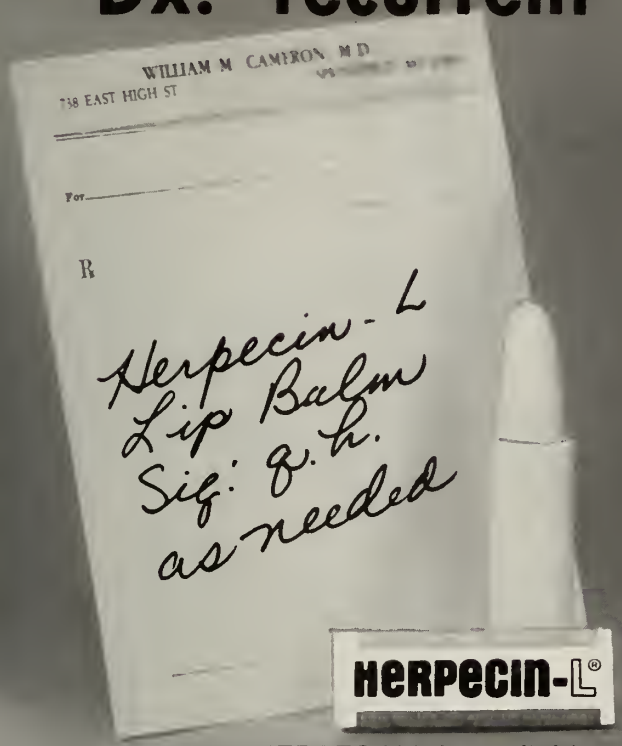
In general, patients with acute or recent myocardial infarction may be more hemodynamically unstable than other patients and should be treated accordingly (see **WARNINGS, Myocardial Infarction**).

On the basis of the pharmacologic actions of Lopressor, the following general measures should be employed.
***Elimination of the Drug:*** Gastric lavage should be performed.
***Bradycardia:*** Atropine should be administered If there is no response to vagal blockade, isoproterenol should be administered cautiously
***Hypotension:*** A vasopressor should be administered, e.g , levarterenol or dopamine
***Bronchospasm:*** A beta$_2$-stimulating agent and/or a theophylline derivative should be administered
***Cardiac Failure:*** A digitalis glycoside and diuretic should be administered. In shock resulting from inadequate cardiac contractility, administration of dobutamine, isoproterenol, or glucagon may be considered

**Geigy** GEIGY Pharmaceuticals
Division of CIBA-GEIGY Corporation
Ardsley, New York 10502

© 1986, Geigy. (9/86) 536-8180-A 8 C86-36 (Rev. 6/86)

# Dx: recurrent herpes labialis




"HERPECIN-L is my **treatment of choice** for perioral herpes." GP, NY

"HERPECIN-L appears to actually **prevent** the blisters . . . used **soon enough.**" DDS, MN

"HERPECIN-L®. . . a **conservative approach** with **low risk/high benefits.**" MD, FL

"Used at **prodromal symptoms** . . . blisters **never formed** . . . remarkable." DH, MA

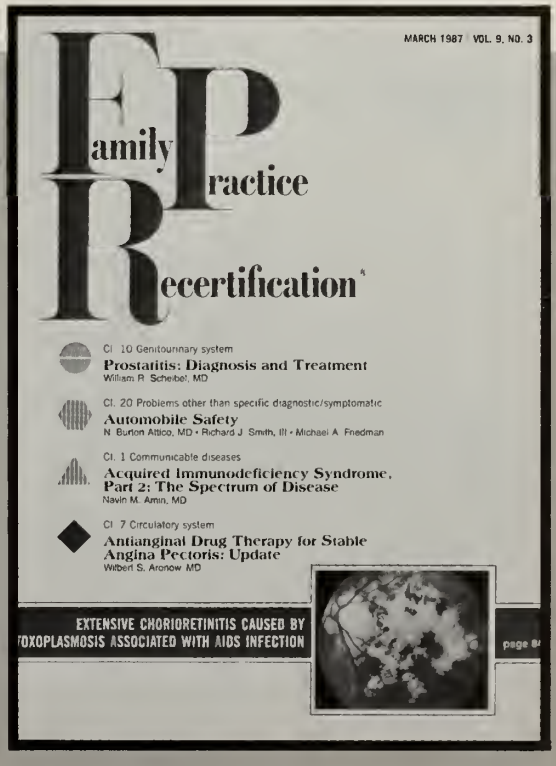
"(In clinical trials) . . . **response** was **dramatic. HERPECIN-L** . . proven **far superior.**" DDS, PA

"All patients claimed **shorter duration** . . . at **prodromal symptoms** . . . HERPECIN-L **averted** the attacks." MD, AK

OTC. *See P.D.R.* for information. For samples to make your own clinical evaluation, write: **CAMPBELL LABORATORIES, INC.**, P.O. BOX 812-MD, FDR STATION, NEW YORK, N.Y. 10150

In the West HERPECIN-L is available at all *Fred Meyer/Grand Central, Osco/Skaggs, Pay 'n Save, Revco, Sav-On, SupeRx and Thrifty* and other select pharmacies.

# The complete journal for family practice physicians




- Reaches 79,000 family physicians monthly
- Presents the most commonly seen patient problems in family practice
- Written by physicians for physicians
- The most current clinical updates in:

| | |
|---|---|
| Cardiology | Ob/Gyn |
| Diabetes | Psychiatry |
| Pediatrics | Gastroenterology |

- Provides 20 hours of CME Category 1 Credit

**PRACTICAL • CLINICAL • EDUCATIONAL • CURRENT**

# The Only Microencapsulated KCl Delivery System That Delivers Both 8mEq K & 10mEq K

## MICRO·K®
(Potassium Chloride)
*Controlled-Release Extencaps® 600 mg (8 mEq K)*

## MICRO·K® 10
(Potassium Chloride)
*Controlled-Release Extencaps® 750 mg (10 mEq K)*

A·H·ROBINS

Pharmaceutical Division, Richmond, Virginia 23261-6609
Member of Certified Medical Representatives Institute
©A.H. Robins Company 1986

The Western Journal of Medicine

VOLUME 146 • NUMBER 5 • MAY 1987

# CONTENTS


## CLINICAL INVESTIGATION

571 **Serum Potassium Concentration in Hyperglycemia of Diabetes Mellitus With Long-term Dialysis**
ANTONIOS H. TZAMALOUKAS, MD, and PRATAP S. AVASTHI, MD
*From the Division of Nephrology, Department of Medicine, Veterans Administration Medical Center and University of New Mexico School of Medicine, Albuquerque.*

## CLINICAL MEDICINE

576 **Use of Intravenous Pyelography in Blunt Trauma—A Reappraisal**
JEROME R. HOFFMAN, MD; ROBERT R. SIMON, MD; MARC SMITH; GLENN STROM, and LARRY J. BARAFF, MD
*From the Departments of Medicine and Pediatrics, Division of Emergency Medicine, Center for the Health Sciences, UCLA School of Medicine, Los Angeles.*

580 **A Practical Approach to Improving Pain Control in Cancer Patients**
MALCOLM L. BRIGDEN, MD, and JEFFREY B. BARNETT, BScPharm
*From the Division of Medical Oncology, Victoria Cancer Clinic (Cancer Control Agency of British Columbia), Royal Jubilee Hospital, Victoria, British Columbia.*

## MEDICAL PROGRESS

585 **Hypoglycemic Syndrome in Infancy and Childhood—A Surgeon's Perspective**
A. R. MOOSA, MD; LORI BAKER, MD, and M. LAVELLE-JONES, MD
*From the Department of Surgery, University of California, San Diego.*

## CLINICOPATHOLOGIC CONFERENCE

589 **Multiple Cerebral Emboli in a Young Man**
MARK P. NESPECA, MD, and JEANNETTE J. TOWNSEND, MD
*From the Departments of Neurology and Pathology, University of Utah School of Medicine, Salt Lake City.*

596 **Editorial Comment: Stroke in Young People—The Heart of the Matter**
ROBERT G. HART, MD, and GREGORY L. FREEMAN, MD
*From the Department of Medicine, University of Texas Health Science Center, San Antonio.*

## MEDICAL STAFF CONFERENCE

598 **Acute Pancreatitis**
Discussants: JAMES H. GRENDELL, MD, and JAMES EGAN, MD
*A discussion selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco, School of Medicine. Taken from a transcription, it was prepared by Drs Homer A. Boushey, Associate Professor of Medicine, and David G. Warnock, Associate Professor of Medicine, under the direction of Dr Lloyd H. Smith, Jr, Professor of Medicine and Associate Dean in the School of Medicine.*

## EPITOMES—IMPORTANT ADVANCES IN CLINICAL MEDICINE

**Emergency Medicine**
*Items of progress in emergency medicine. Each item in the judgment of a panel of knowledgeable physicians has recently become reasonably firmly established, both as to scientific fact and important clinical significance.*

603 **Intraosseous Infusion for Emergency Vascular Access**
JUDITH C. BRILLMAN, MD

603 **Sodium Bicarbonate Therapy in Cardiac Arrest**
RICARDO MARTINEZ, MD

604 **Frostbite**
MICHAEL BARMACHE, MD

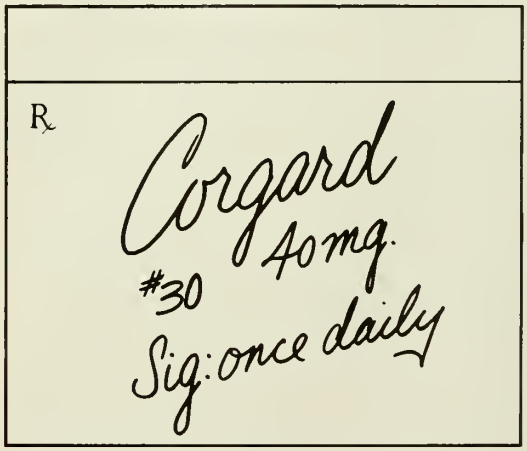
604 **Ibuprofen Overdose**
BRENT T. BURTON, MD

605 **Transcutaneous Cardiac Pacing**
KENNETH J. RHEE, MD


*(Continued on Page 550)*

# CORGARD®
## (nadolol tablets)

## *Advantages beyond control for the hypertensive patient*




**CORGARD® TABLETS**
**Nadolol Tablets**

**DESCRIPTION:** CORGARD (nadolol) is a synthetic non-selective beta-adrenergic receptor blocking agent.

**CONTRAINDICATIONS:** Bronchial asthma, sinus bradycardia and greater than first degree conduction block, cardiogenic shock, and overt cardiac failure (see WARNINGS).

**WARNINGS: Cardiac Failure**—Sympathetic stimulation may be a vital component supporting circulatory function in congestive heart failure, and its inhibition by beta-blockade may precipitate more severe failure. Although beta-blockers should be avoided in overt congestive heart failure, if necessary, they can be used with caution in patients with a history of failure who are well-compensated, usually with digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle. IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta-blockers can, in some cases, lead to cardiac failure; therefore, at first sign or symptom of heart failure, digitalize and/or give diuretics, and closely observe response, or discontinue nadolol (gradually if possible).

**Exacerbation of Ischemic Heart Disease Following Abrupt Withdrawal**—Hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred after *abrupt* discontinuation of such therapy. When discontinuing chronic use of nadolol, particularly in patients with ischemic heart disease, gradually reduce dosage over a 1- to 2- week period and carefully monitor the patient. Reinstitute nadolol promptly (at least temporarily) and take other measures appropriate for management of unstable angina if angina markedly worsens or acute coronary insufficiency develops. Warn patients not to interrupt or discontinue therapy without physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue nadolol therapy abruptly even in patients treated only for hypertension.

**Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema)**—PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA-BLOCKERS. Administer nadolol with caution since it may block bronchodilation produced by endogenous or exogenous catecholamine stimulation of beta$_2$ receptors.

**Major Surgery**—Because beta blockade impairs the ability of the heart to respond to reflex stimuli and may increase risks of general anesthesia and surgical procedures, resulting in protracted hypotension or low cardiac output, it has generally been suggested that such therapy should be withdrawn several days prior to surgery. Recognition of the increased sensitivity to catecholamines of patients recently withdrawn from beta-blocker therapy, however, has made this recommendation controversial. If possible, withdraw beta-blockers well before surgery takes place. In emergency surgery, inform the anesthesiologist that the patient is on beta-blocker therapy. Use of beta-receptor agonists such as isoproterenol, dopamine, dobutamine, or levarterenol can reverse the effects of nadolol. Difficulty in restarting and maintaining the heart beat has also been reported with beta-adrenergic receptor blocking agents.

**Diabetes and Hypoglycemia**—Beta-adrenergic blockade may prevent the appearance of premonitory signs and symptoms (e.g., tachycardia and blood pressure changes) of acute hypoglycemia. This is especially important with labile diabetics. Beta-blockade also reduces release of insulin in response to hyperglycemia; therefore, it may be necessary to adjust dose of antidiabetic drugs.

**Thyrotoxicosis**—Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. To avoid abrupt withdrawal of beta-adrenergic blockade which might precipitate a thyroid storm, carefully manage patients suspected of developing thyrotoxicosis.

**PRECAUTIONS: Impaired Renal Function**—Use nadolol with caution (see DOSAGE AND ADMINISTRATION section of package insert).

**Information for Patients**—Warn patients, especially those with evidence of coronary artery insufficiency, against interruption or discontinuation of nadolol without physician's advice. Although cardiac failure rarely occurs in properly selected patients, advise patients being treated with beta-adrenergic blocking agents to consult physician at first sign of impending failure. Advise patients in event of missed doses.

**Drug Interactions**—Concurrent administration may result in interactions with: Anesthetics, general—exaggeration of the hypotension induced by general anesthetics (see WARNINGS, Major Surgery). Antidiabetic drugs (oral agents and insulin)—hypoglycemia or hyperglycemia; adjust antidiabetic drug dosage accordingly (see WARNINGS, Diabetes and Hypoglycemia). Catecholamine-depleting drugs (e.g., reserpine)—additive effect; monitor closely for hypotension and/or excessive bradycardia.

**Carcinogenesis, Mutagenesis, Impairment of Fertility**—In 1 to 2 years oral toxicologic studies in mice, rats, and dogs, nadolol did not produce significant toxic effects. In 2-year oral carcinogenic studies in rats and mice, nadolol did not produce neoplastic, preneoplastic, or nonneoplastic pathologic lesions.

**Pregnancy Category C**—In animal reproduction studies with nadolol, evidence of embryo- and fetotoxicity was found in rabbits (but not in rats or hamsters) at doses 5 to 10 times greater (on a mg/kg basis) than maximum indicated human dose; no teratogenic potential was seen in any of these species. There are no well-controlled studies in pregnant women; therefore, use nadolol in pregnant women only if potential benefit justifies potential risk to the fetus. Neonates of mothers who received nadolol at parturition have exhibited bradycardia, hypoglycemia and associated symptoms.

**Nursing Mothers**—Nadolol is excreted in human milk. Exercise caution when nadolol is administered to a nursing woman.

**Pediatric Use**—Safety and effectiveness in children have not been established.

**ADVERSE REACTIONS:** Most adverse effects have been mild and transient and have rarely required nadolol withdrawal.

**Cardiovascular**—Bradycardia with heart rates of less than 60 beats per minute occurs commonly, and heart rates below 40 beats per minute and/or symptomatic bradycardia were seen in about 2 of 100 patients. Symptoms of peripheral vascular insufficiency, usually of the Raynaud type, have occurred in approximately 2 of 100 patients. Cardiac failure, hypotension, and rhythm/conduction disturbances have each occurred in about 1 of 100 patients. Single instances of first degree and third degree heart block have been reported; intensification of AV block is a known effect of beta-blockers (see also CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS). **Central Nervous System**—Dizziness or fatigue reported in approximately 2 of 100 patients; paresthesias, sedation, and change in behavior reported in approximately 6 of 1000 patients. **Respiratory**—Bronchospasm reported in approximately 1 of 1000 patients (see CONTRAINDICATIONS and WARNINGS). **Gastrointestinal**—Nausea, diarrhea, abdominal discomfort, constipation, vomiting, indigestion, anorexia, bloating, and flatulence each reported in 1 to 5 of 1000 patients. **Miscellaneous**—Each of the following reported in 1 to 5 of 1000 patients: rash; pruritus; headache; dry mouth, eyes, or skin; impotence or decreased libido; facial swelling; weight gain; slurred speech; cough; nasal stuffiness; sweating; tinnitus; blurred vision; infrequent reversible alopecia.

The following adverse reactions have been reported in patients taking nadolol and/or other beta-adrenergic blocking agents, but no causal relationship to nadolol has been established. **Central Nervous System**—reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place; short-term memory loss, emotional lability with slightly clouded sensorium; decreased performance on neuropsychometrics. **Gastrointestinal**—mesenteric arterial thrombosis; ischemic colitis; elevated liver enzymes. **Hematologic**—agranulocytosis; thrombocytopenic or nonthrombocytopenic purpura. **Allergic**—fever combined with aching and sore throat; laryngospasm; respiratory distress. **Miscellaneous**—pemphigoid rash; hypertensive reaction in patients with pheochromocytoma; sleep disturbances; Peyronie's disease. The oculomucocutaneous syndrome associated with practolol has not been reported with nadolol.

**OVERDOSAGE:** Nadolol can be removed from the general circulation by hemodialysis. In addition to gastric lavage, employ the following measures as appropriate. In determining duration of corrective therapy, take note of long duration of effect of nadolol.

**Excessive Bradycardia**—Administer atropine (0.25 to 1.0 mg). If there is no response to vagal blockade, administer isoproterenol cautiously.

**Cardiac Failure**—Administer a digitalis glycoside and diuretic. It has been reported that glucagon may also be useful in this situation.

**Hypotension**—Administer vasopressors, e.g., epinephrine or levarterenol. (There is evidence that epinephrine may be the drug of choice.)

**Bronchospasm**—Administer a beta$_2$-stimulating agent and/or a theophylline derivative.

**DOSAGE**—For all patients, DOSAGE MUST BE INDIVIDUALIZED.

For **angina pectoris,** usual initial dose is 40 mg q.d.; may be gradually increased in 40 to 80 mg increments at 3 to 7 day intervals until optimum clinical response or pronounced slowing of the heart rate; usual maintenance dose is 40 or 80 mg q.d. (doses up to 160 or 240 mg daily may be needed). If treatment is to be discontinued, reduce dosage gradually over a period of 1 to 2 weeks (see WARNINGS).

For **hypertension,** usual initial dose is 40 mg q.d.; gradually increase in 40 to 80 mg increments until optimum blood pressure reduction is achieved; usual maintenance dose is 40 or 80 mg q.d. (doses up to 240 or 320 mg daily may be needed).

Patients with renal failure require adjustment in dosing interval; see package insert for dosage in these patients.

**For full prescribing information consult package insert.**

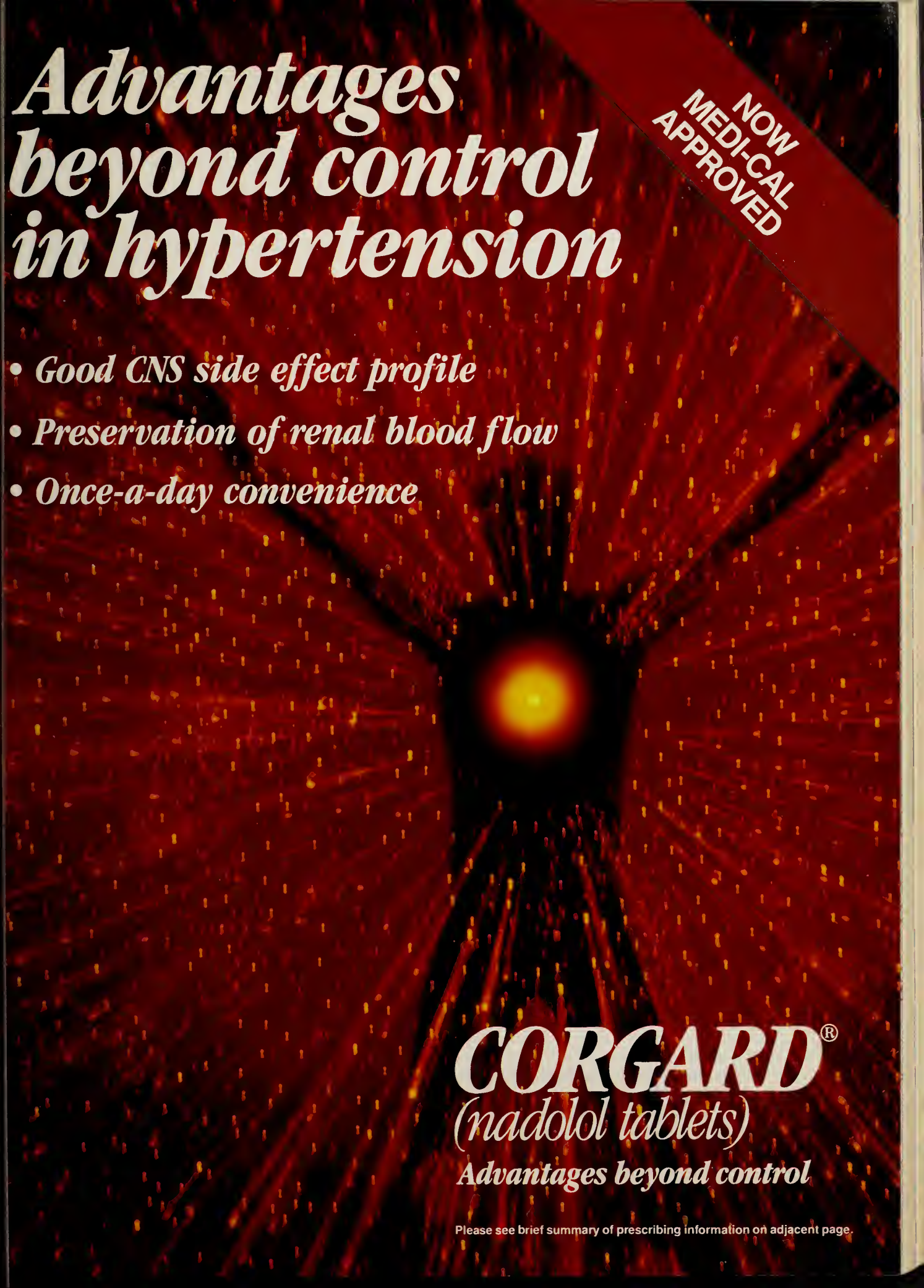
**HOW SUPPLIED:** In scored tablets containing 40, 80, 120, or 160 mg nadolol per tablet in bottles of 100 and in Unimatic® unit-dose packs of 100 tablets. The 40 mg, 80 mg, and 120 mg potencies are also available in bottles of 1000 tablets. (J3-527E)

PRINCETON PHARMACEUTICAL PRODUCTS
A SQUIBB COMPANY

©1987 E.R. Squibb & Sons, Inc., Princeton, NJ

517-534A

Issued: January 1987


Advantages beyond control in hypertension
NOW MEDI-CAL APPROVED
• Good CNS side effect profile
• Preservation of renal blood flow
• Once-a-day convenience
CORGARD®
(nadolol tablets)
Advantages beyond control
Please see brief summary of prescribing information on adjacent page.

(Continued from Page 547)

605 **Evaluating Patients With Tricyclic Antidepressant Overdose for Risk of Complications**
GARRETT E. FOULKE, MD, and MICHAEL CALLAHAM, MD

606 **Treatment of Snakebite**
ROBERT W. DERLET, MD, and GARRETT E. FOULKE, MD

606 **Clinical Uses for a New ß-Lactamase Inhibitor Antibiotic**
DAVID A. TALAN, MD

607 **Cephalosporins for Bacterial Meningitis**
GARY P. YOUNG, MD

608 **Indications for Hyperbaric Oxygen Therapy**
IRVING JACOBY, MD

608 **Cardiopulmonary Resuscitation and Defibrillation**
MICKEY EISENBERG, MD

609 **Expanding the Use of Automatic External Defibrillators to Home and Community**
RICHARD O. CUMMINS, MD

609 **Advances in Radiologic Evaluation of Acute Spinal Cord Compression**
ROBERT L. GALLI, MD

610 **Computed Tomography Versus Peritoneal Lavage in Blunt Abdominal Trauma**
MICHAEL J. BRESLER, MD

610 **Digoxin-Specific Fab Fragments**
GEORGE STERNBACH, MD

## EDITORIALS

612 **Whatever Happened to Report MM?**

612 **The Surgeon's Approach to Hypoglycemia in Infants and Children**
JOHN R. CAMPBELL, MD
*From the Division of Pediatric Surgery, Department of Surgery, Oregon Health Sciences University School of Medicine, Portland.*

613 **Primary Care—Does It Have a Future?**

## CASE REPORTS

614 **The Corticotropin-Releasing Factor Test in the Diagnosis of Ectopic ACTH Secretion**
ENRICO CAGLIERO, MD, and MARA LORENZI, MD
*From the Department of Medicine, Division of Endocrinology and Metabolism, University of California, San Diego, Medical Center.*

615 **Acquired Immunodeficiency Syndrome Presenting as Schizophrenia**
MICHAEL A. CUMMINGS, MD; KATHRYN L. CUMMINGS, RN; MARK H. RAPAPORT, MD; JOSEPH H. ATKINSON, MD, and IGOR GRANT, MD
*From the Department of Psychiatry, Veterans Administration Medical Center, San Diego, and the Department of Psychiatry, University of California, San Diego, School of Medicine, La Jolla.*

618 **A 32-Year-Old Man With the Acquired Immunodeficiency Syndrome and Pneumococcal Meningitis**
DIANE V. HAVLIR, MD; MALLORY D. WITT, MD, and MERLE SANDE, MD
*From the Department of Medicine, Moffitt Hospital, University of California, San Francisco, School of Medicine, and San Francisco General Hospital Medical Center.*

## CORRESPONDENCE

620 **Alcohol and Other Drug Dependence Among Latinos**
P. JOSEPH FRAWLEY, MD

620 **Donor Notification for Positive Non-A, Non-B Hepatitis Surrogate Testing**
DANIEL B. BRUBAKER, DO; SUSIE UKKESTAD, and BYRON A. MYHRE, MD, PhD

620 **The Achilles Heel of Computer-Initiated Bibliographic Search**
ANTONIOS H. TZAMALOUKAS, MD

621 **Dietary Cholesterol and Atherosclerosis**
RALPH S. WOLFSTEIN, MD
SUSAN D. DESMOND, MD, Replies

(Continued on Page 564)

# MPM-1000

## MEDICAL PRACTICE MANAGEMENT SYSTEM

THE COMPLETE PRESCRIPTION FOR OFFICE PRODUCTIVITY FROM CURTIS 1000 INFORMATION SYSTEMS

**$R_x$ for Improved Patient Care...**
MPM-1000 speeds handling of individual patient information with Patient Registration, Patient Billing, Electronic Claims and Hospital/ Physician Network.

**$R_x$ for Profitability...**
MPM-1000 organizes financial data with Accounts Payable, General Ledger and Payroll.

**$R_x$ for Efficiency...**
MPM-1000 controls daily office functions with Word Processing, Medical Dictionary, and Inventory Control.

**$R_x$ for Productivity...**
MPM-1000 allows in-office review of on-line clinical data through Remote Data Base Access and extensive management reporting with Query Report Generator.

Whether you're just starting your medical office or belong to a rapidly growing practice, MPM-1000 is a complete Medical Practice Management System designed to meet your needs now and in the future.

**For more information call or write:**
**Curtis 1000 Information Systems**
Western Regional Office
7011 Cort Rosa, P.O. Box 141
Pleasanton, CA 94566
**(415) 484-2036** or **1-800-241-4780**

Curtis 1000 INFORMATION SYSTEMS

Western Regional Office
7011 Cort Rosa
P.O. Box 141
Pleasanton, CA 94566

Please tell me more about your Prescription for Productivity

Name: _____

Practice Name: _____

Address: _____

City: _____ State _____ Zip _____

Phone: _____ Specialty: _____

Number of Physicians: _____

MPM 1000 MEDICAL PRACTICE MANAGEMENT SYSTEM

# Practice of Sleep Disorders Medicine– State of the Art 1987

## Sept. 10–13

Association of Sleep Disorders Centers
Clinical Sleep Society

Annual Meeting and
Postgraduate Course
San Francisco, California

- Sleep Apnea Syndrome
  Who should be treated and how?
- Insomnia—Diagnosis and management
- Sleep Disorders in the very young
- Sleep Disorders in the elderly
- Alertness in the Workplace—Medical considerations
- Abnormal movements during sleep
- Daytime sleepiness—Diagnosis and treatment

These topics and many more will be covered in depth by the leading authorities in Sleep Disorders Medicine

*For further information contact:*
Association of Sleep Disorders Centers/
Clinical Sleep Society
605 Second Street SW
Rochester, MN 55902
(507) 287-6006



# Books Received

*Books received by* THE WESTERN JOURNAL OF MEDICINE *are acknowledged in this column. Selections will be made for more extensive review in the interest of readers as space permits.*

**PATHOLOGY OF THE VULVA AND VAGINA**—Volume 9 in **Contemporary Issues in Surgical Pathology**—Edited by Edward J. Wilkinson, MD, Professor of Pathology and Obstetrics and Gynecology, University of Florida College of Medicine, and Director, Sections of Gynecological Pathology and Cytopathology, Shands Hospital, Gainesville, Florida. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1986. 328 pages, $55

**PLASTIC SURGERY OF THE HEAD AND NECK**—2 Volumes—Edited by Richard Boies Stark, MD, Professor of Clinical Surgery, Columbia University College of Physicians and Surgeons, and Founder and Attending Surgeon, Plastic Surgery Service, St Luke's-Roosevelt Hospital Center, New York. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1986. 1,480 pages, $275.

**PRINCIPLES OF EXERCISE TESTING AND INTERPRETATION**—Karlman Wasserman, MD, PhD; James E. Hansen, MD; Darryl Y. Sue, MD, and Brian J. Whipp, PhD, DSc, Division of Respiratory Physiology and Medicine, Department of Medicine, Harbor-UCLA Medical Center, Torrance, California. Lea & Febiger, 600 Washington Square, Philadelphia, PA 19106-9982, 1987. 268 pages, $39.50.

**RADIOLOGY OF THE ACUTE ABDOMEN**—Jovitas Skucas, MD, Professor of Radiology, and Robert F. Spataro, MD, Associate Professor of Radiology and Urology, University of Rochester School of Medicine and Dentistry, Strong Memorial Hospital, Rochester, New York. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1986. 697 pages, $125.

**RISK MANAGEMENT AND QUALITY ASSURANCE: ISSUES AND INTERACTIONS**—Edited by Greg Chapman-Cliburn. Quality Review Bulletin, Joint Commission on Accreditation of Hospitals, 875 N Michigan Ave, Chicago, IL 60611, 1986. 152 pages, $30 (paperback).

**SCANNING ELECTRON MICROSCOPY OF NORMAL AND ABNORMAL HUMAN SKIN**—Walter H. Wilborn, PhD, Professor of Anatomy and Director; Barbara M. Hyde, MTA, Electron Microscopy Specialist and Research Associate, and Leopoldo F. Montes, MD, Adjunct Professor of Anatomy and Dermatology Research, Electron Microscopy Center, University of South Alabama College of Medicine, Mobile. VCH Publishers, Inc, 220 E 23rd St, Suite 909, New York, NY 10010, 1986. 219 pages, $49.50.

**SEXUALLY TRANSMITTED DISEASES**—Edited by Yehudi M. Felman, MD, MA, MPhil, Clinical Professor of Dermatology, State University of New York, Downstate Medical Center, Brooklyn, and Lecturer in Public Health, Columbia University College of Physicians and Surgeons, School of Public Health, New York. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1986. 315 pages, $65.

**SPINE—STATE OF THE ART REVIEWS—Volume 1—FAILED BACK SURGERY SYNDROME—EVALUATION AND TREATMENT**—Edited by Arthur H. White, MD, Senior Clinical Consultant, San Francisco Orthopedic Residency Program, and Director, St Mary's Spine Center, St Mary's Hospital and Medical Center, San Francisco. Hanley & Belfus, Inc, 210 S 13th St, Philadelphia, PA 19107, 1986. 174 pages, $30 (series of three issues $72).

**TEMPORARY CARDIAC PACING**—Carl E. Bartecchi, MD, Clinical Professor, Departments of Medicine and Family Medicine, University of Colorado School of Medicine, Denver. Precept Press, 160 E Illinois St, Chicago, IL 60611, 1987. 212 pages, $45 (clothbound).

**TRACHEOTOMY**—Edited by Eugene N. Myers, MD, Professor and Chairman; Sylvan E. Stool, MD, Professor of Otolaryngology and Pediatrics, and Jonas T. Johnson, MD, Associate Professor and Vice Chairman, Department of Otolaryngology, University of Pittsburgh School of Medicine, Pittsburgh. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1985. 310 pages, $42.

**TRAUMA IN CHILDREN**—Edited by Randall E. Marcus, MD, Coordinator of Trauma Services and Assistant Professor of Orthopedic Surgery, Case Western Reserve University School of Medicine, and Attending Orthopedic Surgeon, Rainbow Babies and Children's Hospital, Cleveland. Aspen Publishers, Inc, 1600 Research Blvd, Rockville, MD 20850, 1986. 265 pages, $54.

**ULTRASOUND IN PERINATOLOGY**—Volume 19 in **CLINICS IN DIAGNOSTIC ULTRASOUND**—Edited by Nabil F. Maklad, MD, PhD, Professor and Vice Chairman of Radiology and Professor of Obstetrics, Gynecology and Reproductive Sciences, University of Texas Medical School at Houston. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1986. 215 pages, $32.

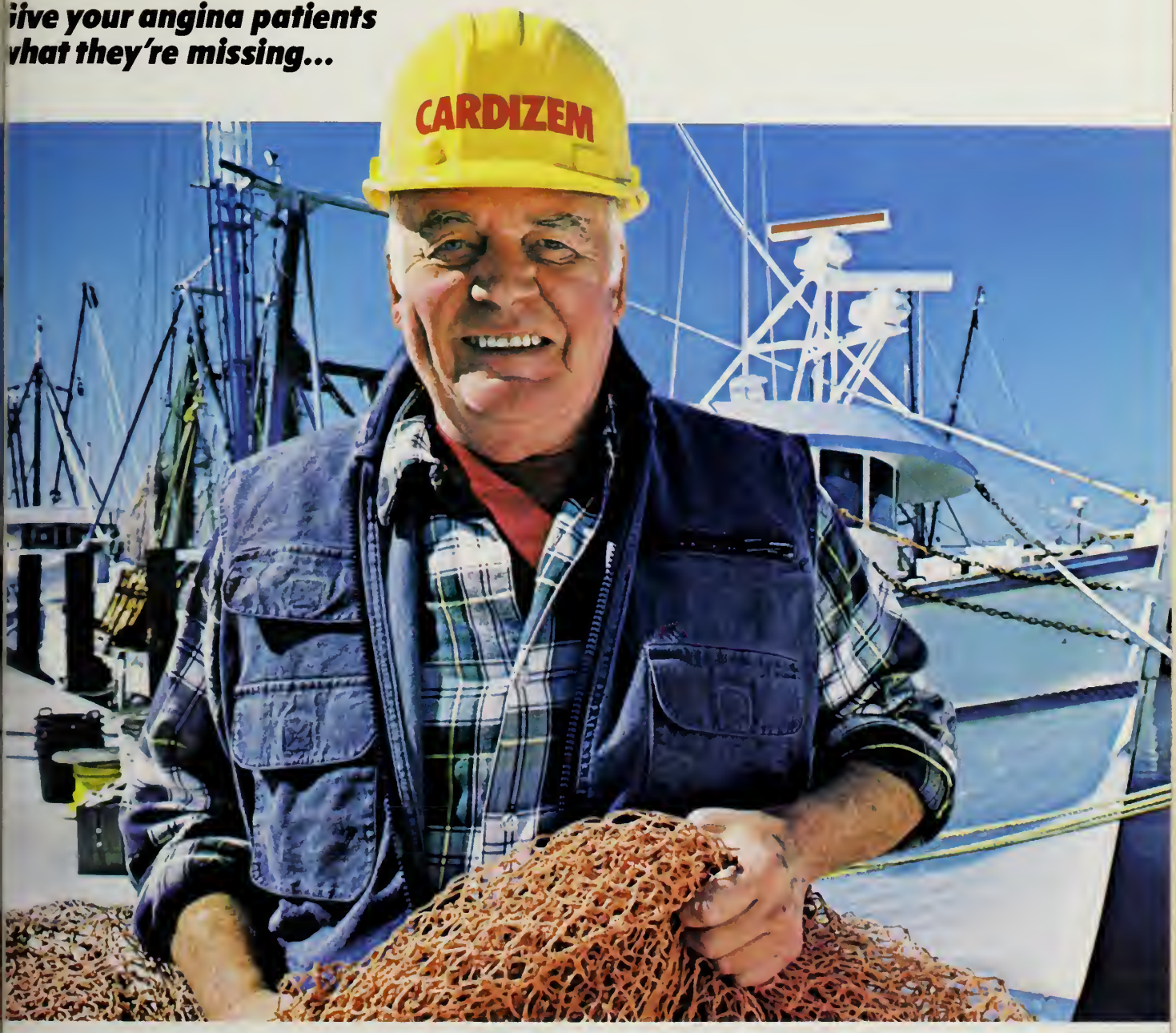
**ULTRASTRUCTURAL APPEARANCES OF TUMOURS—DIAGNOSIS AND CLASSIFICATION OF HUMAN NEOPLASIA BY ELECTRON MICROSCOPY**—Douglas W. Henderson, MB, BS, FRCPA, Director of Electron Microscopy, Flinders Medical Centre, Adelaide, and Honorary Consultant in Ultrastructural Pathology, The Queen Elizabeth Hospital, Woodville, South Australia; John M. Papadimitriou, BA, MD, PhD, MRCPath, FRCPA, Associate Professor of Pathology, The University of Western Australia, and Consultant in Pathology, Royal Perth Hospital and Queen Elizabeth II Medical Centre, Perth, Western Australia, and Mark Coleman, MB, BS, FRCPA, Senior Staff Specialist in Pathology, Flinders Medical Centre, Adelaide, South Australia. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1986. 425 pages, $136.

**WOMEN UNDER THE KNIFE**—Herbert H. Keyser, MD, Associate Clinical Professor of Obstetrics and Gynecology, University of Texas Health Sciences Center, San Antonio. George F. Stickley Company, 210 W. Washington Square, Philadelphia, PA 19106, 1984. 176 pages, $3.95 (in Canada: $4.95).

**WOUND CARE**—William M. Cocke, Jr, MD, Professor of Surgery; Raleigh R. White IV, MD, Professor of Surgery; Dennis J. Lynch, MD, Professor of Surgery and Chief, and Charles N. Verheyden, MD, PhD, Associate Professor of Surgery, Division of Plastic Surgery, Department of Surgery, Scott and White Clinic, Texas A&M University College of Medicine, Temple, Texas. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1986. 113 pages, $25.

**THE WRIST**—Julio Taleisnik, MD, Assistant Clinical Professor of Orthopaedic Surgery, University of California, Irvine, California College of Medicine. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1985. 435 pages, $89.

*ive your angina patients*
*vhat they're missing...*




# CARDIZEM®: FEW SIDE EFFECTS

diltiazem HCl/Marion

- **Antianginal action includes dilatation of coronary arteries, a decrease in vascular resistance/afterload, and a reduction in heart rate**
- **Proven efficacy when used alone in angina[1]**
- **Compatible with other antianginals[2,3]***
- **A safe choice for angina patients with coexisting hypertension, asthma, COPD, or PVD[4,5]**

90 mg NEW 120 mg GREATER DOSAGE FLEXIBILITY

***See Warnings and Precautions.**

*Please see brief summary of prescribing information on the next page.*

# CARDIZEM® FEW SIDE EFFECTS IN ANTIANGINAL THERAPY

diltiazem HCl/Marion

## 60 mg tid or qid

***Brief Summary***
*Professional Use Information*

***CARDIZEM****
*(diltiazem HCl) 30 mg and 60 mg Tablets*

***CONTRAINDICATIONS***

*CARDIZEM is contraindicated in (1) patients with sick sinus syndrome except in the presence of a functioning ventricular pacemaker, (2) patients with second- or third-degree AV block except in the presence of a functioning ventricular pacemaker, and (3) patients with hypotension (less than 90 mm Hg systolic).*

***WARNINGS***

1. ***Cardiac Conduction.*** *CARDIZEM prolongs AV nodal refractory periods without significantly prolonging sinus node recovery time, except in patients with sick sinus syndrome. This effect may rarely result in abnormally slow heart rates (particularly in patients with sick sinus syndrome) or second- or third-degree AV block (six of 1,243 patients for 0.48%). Concomitant use of diltiazem with beta-blockers or digitalis may result in additive effects on cardiac conduction. A patient with Prinzmetal's angina developed periods of asystole (2 to 5 seconds) after a single dose of 60 mg of diltiazem.*
2. ***Congestive Heart Failure.*** *Although diltiazem has a negative inotropic effect in isolated animal tissue preparations, hemodynamic studies in humans with normal ventricular function have not shown a reduction in cardiac index nor consistent negative effects on contractility (dp/dt).*
   *Experience with the use of CARDIZEM alone or in combination with beta-blockers in patients with impaired ventricular function is very limited. Caution should be exercised when using the drug in such patients.*
3. ***Hypotension.*** *Decreases in blood pressure associated with CARDIZEM therapy may occasionally result in symptomatic hypotension.*
4. ***Acute Hepatic Injury.*** *In rare instances, significant elevations in enzymes such as alkaline phosphatase, CPK, LDH, SGOT, SGPT, and other symptoms consistent with acute hepatic injury have been noted. These reactions have been reversible upon discontinuation of drug therapy. The relationship to CARDIZEM is uncertain in most cases, but probable in some. (See PRECAUTIONS.)*

***PRECAUTIONS***

***General.*** *CARDIZEM (diltiazem hydrochloride) is extensively metabolized by the liver and excreted by the kidneys and in bile. As with any new drug given over prolonged periods, laboratory parameters should be monitored at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function. In subacute and chronic dog and rat studies designed to produce toxicity, high doses of diltiazem were associated with hepatic damage. In special subacute hepatic studies, oral doses of 125 mg/kg and higher in rats were associated with histological changes in the liver which were reversible when the drug was discontinued. In dogs, doses of 20 mg/kg were also associated with hepatic changes, however, these changes were reversible with continued dosing.*

***Drug Interaction.*** *Pharmacologic studies indicate that there may be additive effects in prolonging AV conduction when using beta-blockers or digitalis concomitantly with CARDIZEM. (See WARNINGS.)*

*Controlled and uncontrolled domestic studies suggest that concomitant use of CARDIZEM and beta-blockers or digitalis is usually well tolerated. Available data are not sufficient, however, to predict the effects of concomitant treatment, particularly in patients with left ventricular dysfunction or cardiac conduction abnormalities. In healthy volunteers, diltiazem has been shown to increase serum digoxin levels up to 20%.*

***Carcinogenesis, Mutagenesis, Impairment of Fertility.*** *A 24-month study in rats and a 21-month study in mice showed no evidence of carcinogenicity. There was also no mutagenic response in in vitro bacterial tests. No intrinsic effect on fertility was observed in rats.*

***Pregnancy.*** *Category C. Reproduction studies have been conducted in mice, rats, and rabbits. Administration of doses ranging from five to ten times greater (on a mg/kg basis) than the daily recommended therapeutic dose has resulted in embryo and fetal lethality. These doses, in some studies, have been reported to cause skeletal abnormalities. In the perinatal/postnatal studies, there was some reduction in early individual pup weights and survival rates. There was an increased incidence of stillbirths at doses of 20 times the human dose or greater.*

*There are no well-controlled studies in pregnant women; therefore, use CARDIZEM in pregnant women only if the potential benefit justifies the potential risk to the fetus.*

***Nursing Mothers.*** *Diltiazem is excreted in human milk. One report suggests that concentrations in breast milk may approximate serum levels. If use of CARDIZEM is deemed essential, an alternative method of infant feeding should be instituted.*

***Pediatric Use.*** *Safety and effectiveness in children have not been established.*

***ADVERSE REACTIONS***

*Serious adverse reactions have been rare in studies carried out to date, but it should be recognized that patients with impaired ventricular function and cardiac conduction abnormalities have usually been excluded.*

*In domestic placebo-controlled trials, the incidence of adverse reactions reported during CARDIZEM therapy was not greater than that reported during placebo therapy.*

*The following represent occurrences observed in clinical studies which can be at least reasonably associated with the pharmacology of calcium influx inhibition. In many cases, the relationship to CARDIZEM has not been established. The most common occurrences as well as their frequency of presentation are: edema (2.4%), headache (2.1%), nausea (1.9%), dizziness (1.5%), rash (1.3%), asthenia (1.2%). In addition, the following events were reported infrequently (less than 1%):*

| | |
|---|---|
| *Cardiovascular:* | *Angina, arrhythmia, AV block (first degree), AV block (second or third degree — see conduction warning), bradycardia, congestive heart failure, flushing, hypotension, palpitations, syncope* |
| *Nervous System:* | *Amnesia, gait abnormality, hallucinations, insomnia, nervousness, paresthesia, personality change, somnolence, tinnitus, tremor.* |
| *Gastrointestinal:* | *Anorexia, constipation, diarrhea, dysgeusia, dyspepsia, mild elevations of alkaline phosphatase, SGOT, SGPT, and LDH (see hepatic warnings), vomiting, weight increase* |
| *Dermatologic:* | *Petechiae, pruritus, photosensitivity, urticaria.* |
| *Other:* | *Amblyopia, dyspnea, epistaxis, eye irritation, hyperglycemia, nasal congestion, nocturia, osteoarticular pain, polyuria, sexual difficulties.* |

*The following postmarketing events have been reported infrequently in patients receiving CARDIZEM: alopecia, gingival hyperplasia, erythema multiforme, and leukopenia. However, a definitive cause and effect between these events and CARDIZEM therapy is yet to be established.* *Issued 7/86*

*See complete Professional Use Information before prescribing.*

***References:*** ***1.*** *Pepine CJ, Feldman RL, Hill JA, et al: Clinical outcome after treatment of rest angina with calcium blockers: Comparative experience during the initial year of therapy with diltiazem, nifedipine, and verapamil. Am Heart J 1983, 106(6):1341-1347.* ***2.*** *Shapiro W: Calcium channel blockers: Actions on the heart and uses in ischemic heart disease. Consultant 1984,24(Dec):150-159.* ***3.*** *Johnston DL, Lesowoy R, Humen DP, et al: Clinical and hemodynamic evaluation of propranolol in combination with verapamil, nifedipine and diltiazem in exertional angina pectoris: A placebo-controlled, double-blind, randomized, crossover study. Am J Cardiol 1985;55:680-687.* ***4.*** *Cohn PF, Braunwald E: Chronic ischemic heart disease, in Braunwald E (ed): Heart Disease: A Textbook of Cardiovascular Medicine, ed 2. Philadelphia, WB Saunders Co, 1984, chap 39.* ***5.*** *Schroeder JS: Calcium and beta blockers in ischemic heart disease: When to use which. Mod Med 1982;50(Sept):94-116.*

Another patient benefit product from

PHARMACEUTICAL DIVISION
MARION LABORATORIES, INC.
KANSAS CITY MO 64137

0246M6

# The New Look of

# Medrol® Dosepak™ Unit of Use

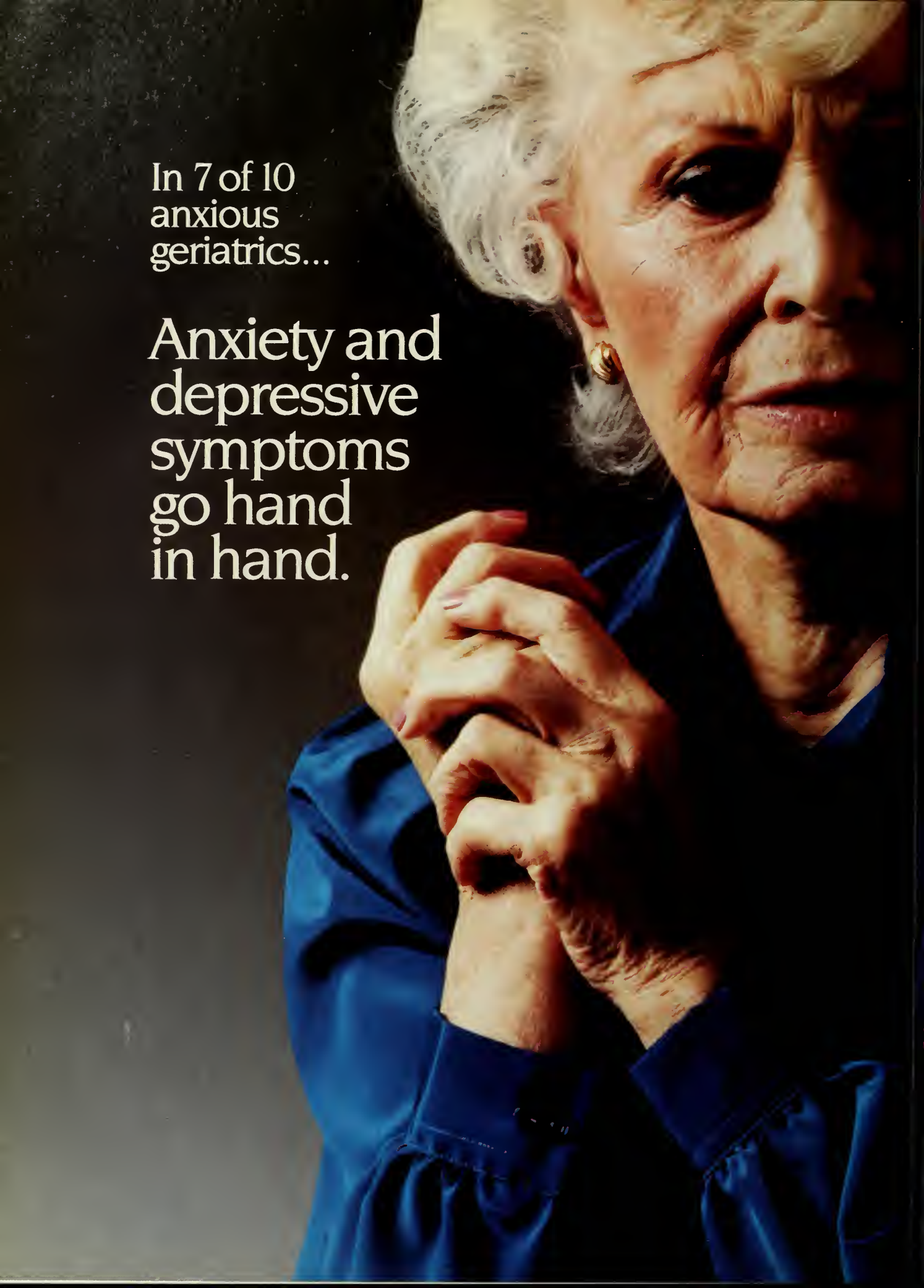
## 4 mg methylprednisolone tablets, USP

The explicit printed dosage instructions that accompany each *Dosepak* make it easy for the patient to understand and follow the dosage regimen.

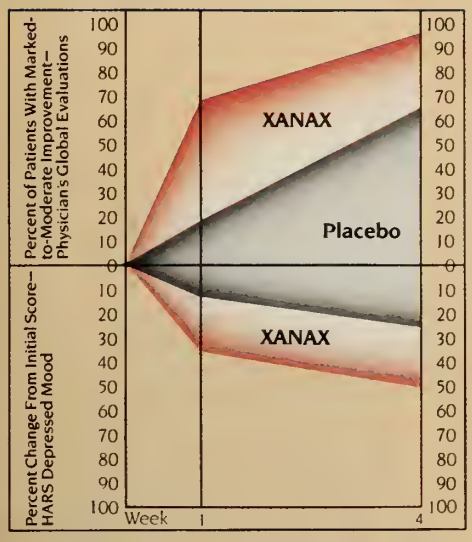
Upjohn 100 A Century of Caring 1886·1986

J-5945RC
January 1986

© 1986 The Upjohn Company


In 7 of 10
anxious
geriatrics...
Anxiety and
depressive
symptoms
go hand
in hand.

# Xanax effectively relieves anxiety with associated depressive symptoms.




In a recent clinical study[1] of 83 geriatric patients with clinical anxiety, 73% were diagnosed as having symptoms of depressed mood.

XANAX is well suited for therapy because it demonstrates greater efficacy than does placebo in reducing the Hamilton Anxiety Rating Scale Total Score and individual items, including depressed mood (see Figure).

# With clinical advantages for geriatric patients.

- Effectively relieves the symptoms of anxiety
- Also relieves anxiety with associated depressed mood
- Well tolerated—side effects, if they occur, are generally observed at the beginning of therapy and usually disappear with continued medication. Drowsiness and light-headedness were the most commonly reported adverse reactions
- Does not cause cardiovascular toxicity
- **Specific geriatric dosage**—0.25 mg, two or three times daily

1. Cohn JB. Double-blind safety and efficacy comparison of alprazolam and placebo in the treatment of anxiety in geriatric patients. *Curr Ther Res* 1984;35(1):100-112

**Xanax®** 0.25 mg Tablets
alprazolam C-IV

**Upjohn**

©1987 The Upjohn Company
Kalamazoo, Michigan 49001, USA

Please see adjacent page for brief summary of prescribing information.

**XANAX® Tablets**
**(alprazolam) ©**

**CONTRAINDICATIONS**
Patients with sensitivity to this drug or other benzodiazepines and in acute narrow angle glaucoma.

**WARNINGS**
Not of value in psychotic patients. Caution patients against hazardous occupations requiring complete mental alertness and about the simultaneous ingestion of alcohol and other CNS depressant drugs.

Benzodiazepines can cause fetal harm in pregnant women. Warn patients of the potential hazard to the fetus. Avoid during the first trimester.

**PRECAUTIONS**
*General:* The dosage of XANAX Tablets should be reduced or withdrawn gradually, since withdrawal seizures have been reported upon abrupt withdrawal. If XANAX is combined with other psychotropics or anticonvulsant drugs, consider drug potentiation (see Drug Interaction section). Exercise the usual precautions regarding size of the prescription for depressed or suicidal patients. In elderly and debilitated patients, use the lowest possible dosage (see Dosage and Administration). Observe the usual precautions in treating patients with impaired renal or hepatic function.

*Information for Patients:* Alert patients about: (a) consumption of alcohol and drugs, (b) possible fetal abnormalities, (c) operating machinery or driving, (d) not increasing dose of the drug due to risk of dependence, (e) not stopping the drug abruptly. *Laboratory Tests:* Not ordinarily required in otherwise healthy patients. *Drug Interactions:* Additive CNS depressant effects with other psychotropics, anticonvulsants, antihistamines, ethanol and other CNS depressants. Pharmacokinetic interactions with other drugs, e.g., cimetidine, have been reported. *Drug/Laboratory Test Interactions:* No consistent pattern for a drug or test. *Carcinogenesis, Mutagenesis, Impairment of Fertility:* No carcinogenic potential or impairment of fertility in rats. *Pregnancy:* See Warnings. *Nonteratogenic Effects:* The child born of a mother on benzodiazepines may be at some risk for withdrawal symptoms and neonatal flaccidity. *Labor and Delivery:* No established use. *Nursing Mothers:* Benzodiazepines are excreted in human milk. Women on XANAX should not nurse. *Pediatric Use:* Safety and effectiveness in children below the age of 18 have not been established.

**ADVERSE REACTIONS**
Side effects are generally observed at the beginning of therapy and usually disappear with continued medication. In the usual patient, the most frequent side effects are likely to be an extension of the pharmacologic activity of XANAX, e.g., drowsiness or lightheadedness.

*Central nervous system:* Drowsiness, lightheadedness, depression, headache, confusion, insomnia, nervousness, syncope, dizziness, akathisia, and tiredness/sleepiness. *Gastrointestinal:* Dry mouth, constipation, diarrhea, nausea/vomiting, and increased salivation. *Cardiovascular:* Tachycardia/palpitations, and hypotension. *Sensory:* Blurred vision. *Musculoskeletal:* Rigidity and tremor. *Cutaneous:* Dermatitis/allergy. *Other side effects:* Nasal congestion, weight gain, and weight loss.

Withdrawal seizures have been reported upon rapid decrease or abrupt discontinuation of XANAX. (See Precautions.)

In addition, the following adverse events have been reported with the use of benzodiazepines: dystonia, irritability, concentration difficulties, anorexia, transient amnesia or memory impairment, loss of coordination, fatigue, sedation, slurred speech, jaundice, musculoskeletal weakness, pruritus, diplopia, dysarthria, changes in libido, menstrual irregularities, incontinence and urinary retention.

Paradoxical reactions such as stimulation, agitation, increased muscle spasticity, sleep disturbances, and hallucinations may occur. Should these occur, discontinue the drug.

During prolonged treatment, periodic blood counts, urinalysis, and blood chemistry analysis are advisable. Minor EEG changes, of unknown significance, have been observed.

**DRUG ABUSE AND DEPENDENCE**
*Physical and Psychological Dependence:* Withdrawal symptoms have occurred following abrupt discontinuance of benzodiazepines. Withdrawal seizures have occurred upon rapid decrease or abrupt discontinuation of therapy. In all patients, dosage should be gradually tapered under close supervision. Patients with a history of seizures or epilepsy should not be abruptly withdrawn from XANAX. Addiction-prone individuals should be under careful surveillance. *Controlled Substance Class:* XANAX is a controlled substance and has been assigned to schedule IV.

**OVERDOSAGE**
Manifestations include somnolence, confusion, impaired coordination, diminished reflexes and coma. No delayed reactions have been reported.

**DOSAGE AND ADMINISTRATION**
Dosage should be individualized.

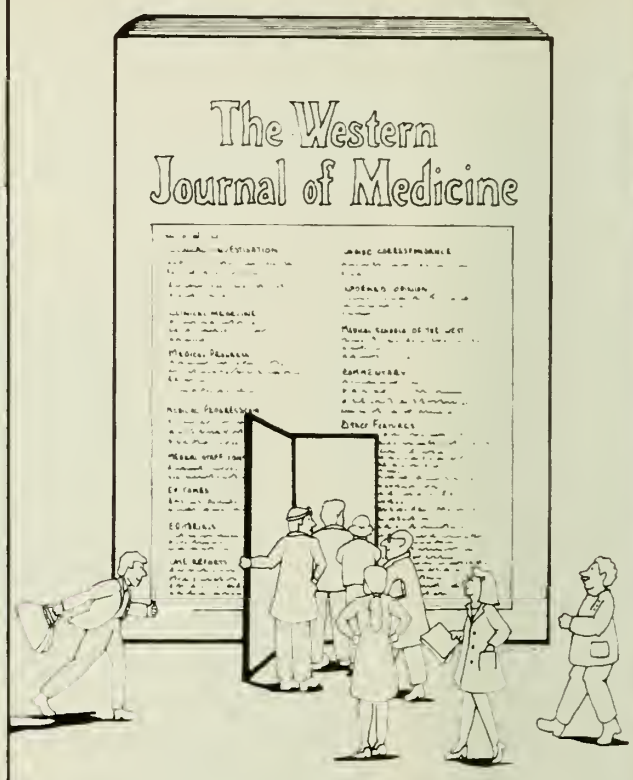
The usual starting dose is 0.25 to 0.5 mg, t.i.d. Maximum total daily dose is 4 mg. In the elderly or debilitated, the usual starting dose is 0.25 mg, two or three times daily. Reduce dosage gradually when terminating therapy, by no more than 0.5 milligram every three days.

**HOW SUPPLIED**
XANAX Tablets are available as 0.25 mg, 0.5 mg, and 1 mg tablets.

**Caution:** Federal law prohibits dispensing without prescription. B-5-S

**Upjohn** THE UPJOHN COMPANY
Kalamazoo, Michigan 49001 USA
J-7382
February 1987






# Inside Information.

WJ5/87

**The Western Journal of Medicine**

Please mail this coupon with enclosed payment to:

**Circulation Department**
P.O. Box 7602, San Francisco,
California 94120-7602

Subscriptions, 12 Issues Per Year
U.S. and Canada $30 1 year,
$50 2 years

All other countries $50 1 year
$90 2 years

Enclosed is $_____ to cover _____ subscriptions.
Send subscription renewal ☐ Regular subscription ☐ Foreign subscription ☐

TO _____

Street _____

City _____ State _____ Zip _____

Gift Card to read "From _____"

# Check our vital signs.

More physicians in California depend upon SCPIE than any other company for their professional liability insurance. There are many reasons why SCPIE is the leader. Check them out:

**Rates:** This is your bottom line. SCPIE rates are highly competitive. "Profits" are returned to the policyholders through Experience Credits.

**Stability:** SCPIE has a history of stable rates and financial strength. SCPIE has adequate reserves to pay anticipated claims, plus surplus to cover unexpected losses. SCPIE is reinsured with Lloyds of London.

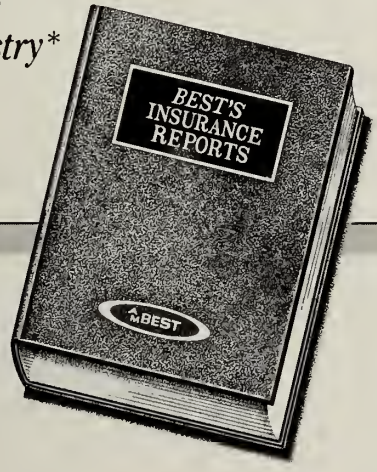
**Non-assessability:** You cannot be assessed if claims experience turns sour. SCPIE is a top-flight *insurance* company, not a cooperative which requires you to assume unlimited liability for others' losses.

**Claims Handling:** A claim is a traumatic experience. You get highly qualified legal counsel, experienced in professional liability claims. Three out of four claims are closed without payment. Our record of defense verdicts is over 85%.

**Underwriting:** Physicians review all applications requesting nose coverage and/or with claims history. SCPIE also maintains an on-going underwriting process to be sure members meet quality standards.

**Local physician control:** SCPIE is owned by its physician policyholders, who elect physicians to run it. They make sure that overhead is low and performance is high.

*A+ Rating from A.M. Best Company, the Bible of the insurance industry**




** SCPIE is one of only five physician-owned companies in the nation to have the Best's A+ rating. We are the largest of them all.*

scpie

Southern California Physicians Insurance Exchange

2029 Century Park East
Suite 2300
Los Angeles, CA 90067
(213) 552-8900

Sponsored by SOCAP: The medical associations and societies of Kern County, Los Angeles County, Orange County, San Bernardino County, San Luis Obispo County, Santa Barbara County and Ventura County.

# Continuing Medical Education

**ARIZONA • CALIFORNIA, HAWAII, NEVADA • IDAHO • MONTANA • NEW MEXICO • UTAH • WASHINGTON • WYOMING**

## ARIZONA

The following list of continuing medical education programs in Arizona is compiled by the Arizona Medical Association. All courses listed have been certified as meeting the criteria for Category I of the ArMA CME Certificate and the AMA Physicians Recognition Award. To list Category I continuing medical education programs, please send information to Arizona Medical Association, 810 West Bethany Home Road, Phoenix, AZ 85013; or phone (602) 246-8901.

Brochures and registration forms are available from the contact person or organization sponsoring the program.

June 4—**Arizona Medical Association Annual Scientific Session.** The Pointe at South Mountain, Phoenix. Thurs. Contact: ArMA.

June 12-14—**Pediatrics in the Red Rocks—10th Annual Summer Pediatrics Conference.** Poco Diablo Resort, Sedona. Fri-Sun. Contact: U of A.

### CONTACT INFORMATION

ArMA—Contact: Arizona Medical Association, 810 W Bethany Home Rd, Phoenix, AZ 85013. (602) 246-8901.

U of A—Contact: University of Arizona College of Medicine, Arizona Health Sciences Center, Tucson, AZ 85724. (602) 626-6707.

## CALIFORNIA, HAWAII AND NEVADA

This listing of continuing education programs in California, Hawaii and Nevada is supplied by the Committee on Continuing Medical Education of the California Medical Association. All courses and meetings listed have been approved for Category I credit toward the CMA Certificate in Continuing Medical Education. To have accredited courses listed here, please send information at least two months in advance to Department of Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690; or phone (415) 863-5522. For a list of organizations approved for Category I credit toward the CMA Certificate in Continuing Medical Education or for more information on accreditation or certification, please write to the above address.

### ANESTHESIOLOGY

June 25-28—**California Society of Anesthesiologists Annual Meeting.** Hotel Inter-Continental, San Diego. Thurs-Sun. 16 hrs. $225. Contact: Linda P. Londerville, 100 S Ellsworth Ave, Ste 806, San Mateo 94401. (415) 348-1407.

August 23-28—**California Society of Anesthesiologists Hawaiian Seminar.** Sheraton Royal Waikoloa Hotel, The Big Island, Hawaii. Sun-Fri. 20 hrs. $375. Contact: Linda P. Londerville, 100 S Ellsworth Ave, Ste 806, San Mateo 94401. (415) 348-1407.

September 12-13—**Case Conference on Clinical Anesthesiology.** California Society of Anesthesiologists at High Sierra Hotel, Lake Tahoe, Nevada. Sat-Sun. 9 hrs. $160. Contact: California Society of Anesthesiologists, 100 S Ellsworth Ave, Ste 806, San Mateo 94401. (415) 348-1407.

October 18-23—**Hawaiian Seminar on Clinical Anesthesia.** California Society of Anesthesiology at Westin Maui, Kaanapali Beach, Hawaii. Sun-Fri. 20 hrs. $375. Contact: California Society of Anesthesiology, 100 S Ellsworth Ave, Ste 806, San Mateo 94401. (415) 348-1407.

### CANCER

September 12—**Advances in Lung Cancer.** UCI at Long Beach. Sat. Contact: UCI.

October 19-21—**11th Annual Cancer Symposium.** Scripps Memorial Hospital at Sheraton Harbor Island Hotel, San Diego. Mon-Wed. 21 hrs. $350. Contact: Nomi Feldman, Scripps Memorial Hospital, 3770 Tansy, San Diego 92121. (619) 453-6222.

### CARDIOLOGY

May 15-17—**Update in Cardiology/Resuscitation.** Superior California Medical Education Council, Redding at Alexander Valley (cycling tour). Fri-Sun. 6 hrs. Contact: J. Bear Co, PO Box 117, Burney 96013. (916) 335-3388.

### KEY TO ABBREVIATIONS

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690. (415) 863-5522.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Herbert M. Thomas, MD, MPH, Director of CME, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th Street, Los Angeles 90059. (213) 603-3183.

LLU: Loma Linda University
Contact: Varner J. Johns, Jr, MD, Associate Dean for Continuing Medical Education, Loma Linda University School of Medicine, Loma Linda 92354. (714) 796-7311, ext 2400.

PMC: Pacific Medical Center
Contact: Continuing Education, Pacific Medical Center, PO Box 7999, San Francisco 94120. (415) 563-4321, ext 2761.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Medical School Office Building, Suite X-365, Stanford 94305-6114. (415) 723-5594.

UCD: University of California, Davis
Contact: Ruth Feryok, Director, Office of Continuing Medical Education, University of California, Davis, School of Medicine, 2701 Stockton Boulevard, Sacramento 95817. (916) 453-5390.

UCI: University of California, Irvine
Contact: Melvin I. Marks, MD, Assistant Dean, University of California, Irvine, California College of Medicine, c/o UCI/CME Program, Memorial Medical Center, 2801 Atlantic Avenue, Long Beach 90801-1428. (213) 595-3811, or (714) 856-5414, UCI Extension.

UCLA: University of California, Los Angeles
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, PO Box 24902, UCLA, Los Angeles 90024. (213) 825-7241.

UCSD: University of California, San Diego
Contact: Office of Continuing Medical Education, University of California, San Diego, School of Medicine (M-017), La Jolla 92093. (619) 534-3713.

UCSF: University of California, San Francisco
Contact: Robert Maggio, Administrative Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 476-4251.

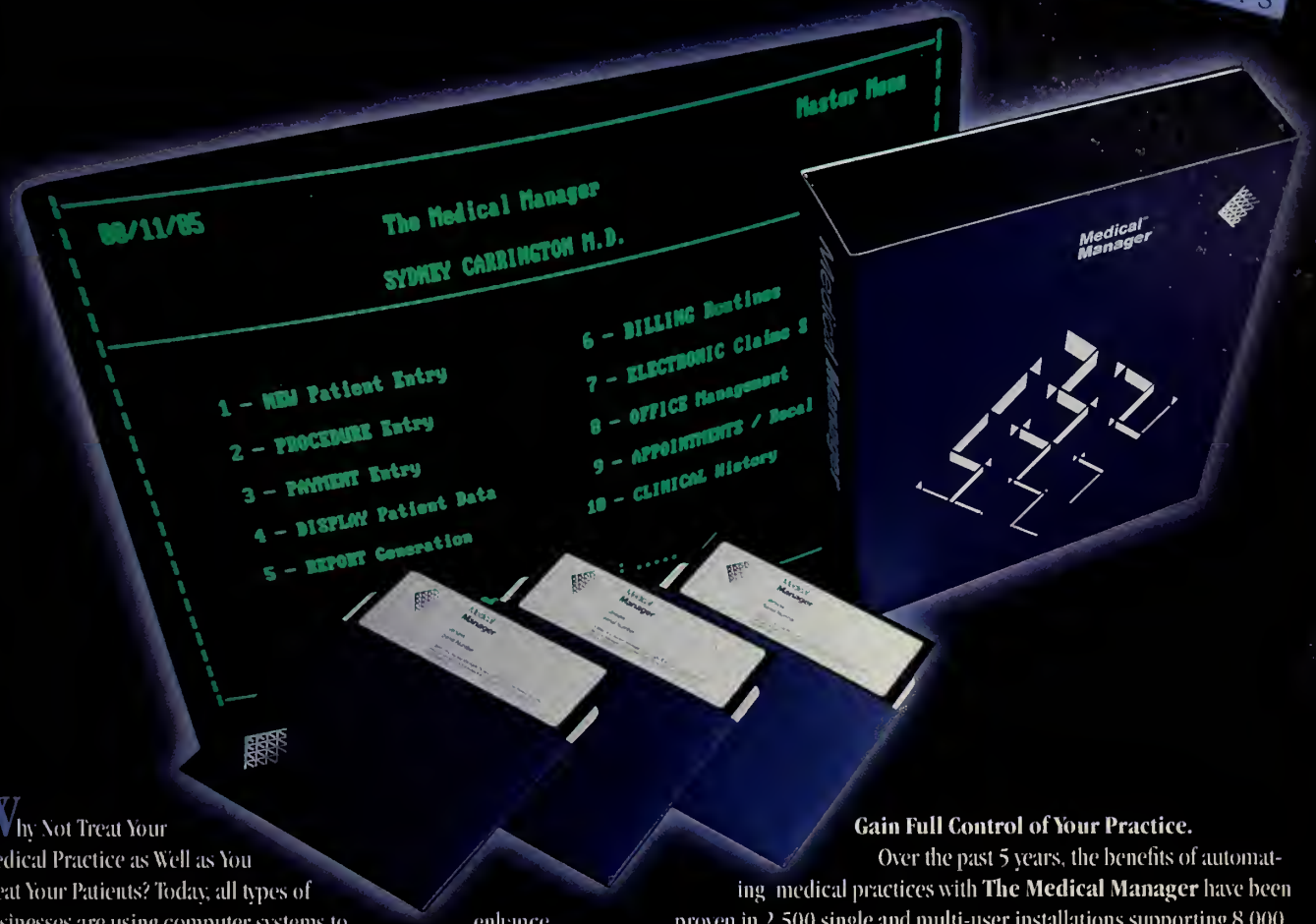
USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 1975 Zonal Ave, KAM314, Los Angeles 90033. (213) 224-7051.

*(Continued on Page 562)*

# Medical Manager®

## Medical Office Management Software

NOW AVAILABLE FOR UNIX SYSTEMS




Why Not Treat Your Medical Practice as Well as You Treat Your Patients? Today, all types of businesses are using computer systems to enhance productivity. As business professionals, more and more physicians are looking to computer systems to dramatically improve productivity and generate timely information for sound financial management and superior patient care.

**Join the Information Revolution.**

Automate your business with a complete medical practice management solution from Systems Plus, Inc. **The Medical Manager** software manages your practice from the moment a new patient calls for an appointment through to billing and patient recall.

- **Comprehensive features** for all aspects of patient communications including encounter forms, insurance billing, outstanding balance follow-up and more...
- **Accountability** — provides sound financial data and clear audit trails based on standard accounting principles.
- **Reporting** — creates detailed office management and financial reports; Custom reports generator.
- **Electronic Media Claims (EMC)** increases cash flow by reducing insurance payment turnaround times. The EMC module submits and tracks insurance claims via modem or diskette to insurance companies nationwide.
- **Flexibility** — supports popular hardware and operating environments including PC-DOS,® Concurrent PC DOS,® Xenix,® Novell NetWare® and Unix.™

**Gain Full Control of Your Practice.**

Over the past 5 years, the benefits of automating medical practices with **The Medical Manager** have been proven in 2,500 single and multi-user installations supporting 8,000 physicians nationwide. Thousands of your colleagues have increased efficiency, productivity, and profitability while gaining tighter control over the day-to-day operations of their businesses.

Find out how Systems Plus, the national leader in computer solutions for practice management, can help you survive in today's competitive medical marketplace by turning your practice into a well-managed business. Contact us on our toll-free lines at **(800) 222-7701 or (800) 222-7707 in California** for more information and the name of your local representative. Mention this ad and receive a **free** copy of our Medical Manager features and reports manual.

**Systems Plus, Inc.®**
500 Clyde Avenue
Mountain, View, CA 94043
(415) 969-7047

Systems Plus is a registered trademark of Systems Plus, Inc. • Medical Manager is a registered trademark of Personalized Programming, Inc. • Unix is a trademark of AT&T Bell Lab. • Novell NetWare is a registered trademark of Novell, Inc. • PC DOS is a registered trademark of IBM. • Concurrent PC DOS is a registered trademark of Digital Research, Inc. • Xenix is a registered trademark of Microsoft Corporation.

CONTINUING MEDICAL EDUCATION

(Continued from Page 560)

May 24-30—**5th Annual Cardiology Update.** Institute for Medical Studies at Honolulu, Hawaii. Sun-Sat. 26 hrs. $395. Contact: Lisa Krehbiel, Inst for Med Studies, 30131 Town Ctr Dr, Ste 215, Laguna Niguel 92677. (714) 495-4499.

June 7-10—**Critical Examination Review Course.** American College of Chest Physicians at Hotel Del Coronado, Coronado. Sun-Wed. 30 hrs. $575. Contact: ACCP, PO Box 93826, Chicago, IL 60673. (312) 698-2200.

June 10—**Cardiology: Arrhythmias.** LLU at LLU. Wed. 4 hrs. $60. Contact: LLU.

June 10-13—**Advanced Echocardiography and Doppler Ultrasound—1987.** American College of Cardiology at Sheraton Harbor Island East, San Diego. Wed-Sat. Contact: Mary Anne McInerny, ACC, 9111 Old Georgetown Rd, Bethesda, MD 20814. (301) 897-5400, ext 226.

June 18-20—**Coronary Heart Disease: Current Concepts.** Medical Education Resources at Sheraton Waikiki Hotel, Honolulu, Hawaii. Thurs-Sat. 11 hrs. $295. Contact: Debbie Wilderson, Medical Education Resources, 5808 S Rapp St, Ste 202, Littleton, CO 80120. (800) 421-3756.

June 25-27—**Consultative Cardiology: Update in Diagnostic and Therapeutic Techniques.** American College of Cardiology at Westin South Coast Hotel, Costa Mesa. Thurs-Sat. Contact: Mary Anne McInerny, ACC, 9111 Old Georgetown Rd, Bethesda, MD 20814. (301) 897-5400, ext 226.

July 17-18—**Coronary Heart Disease: Current Concepts.** Medical Education Resources at Sheraton Hotel, Anaheim. Fri-Sat. 11 hrs. $295. Contact: Debbie Wilderson, 5808 S Rapp St, Ste 202, Littleton, CO 80120. (800) 421-3756.

July 31-August 1—**Arrhythmias: Interpretation, Diagnosis, and Management.** Medical Education Resources at Harvey's Hotel, Lake Tahoe, Nevada. Fri-Sat. 11 hrs. $295. Contact: Debbie Wilderson, 5808 S Rapp St, Ste 202, Littleton, CO 80120. (800) 421-3756.

August 2-7—**Current Concepts in Cardiology.** UCD at Hyatt Lake Tahoe, Incline Village, Nevada. Sun-Fri. Contact: UCD.

August 7-8—**Coronary Heart Disease: Current Concepts.** Medical Education Resources at Doubletree Inn, Monterey. Fri-Sat. 11 hrs. $295. Contact: Debbie Wilderson, 5808 S Rapp St, Ste 202, Littleton, CO 80120. (800) 421-3756 or (303) 798-9682.

September 18-20—**Diagnosis and Management of Respiratory Diseases.** Medical Education Resources at Tropicana Hotel, Las Vegas, Nevada. Fri-Sun. 13 hrs. $295. Contact: Medical Education Resources, 5808 S Rapp St, Ste 202, Littleton, CO 80120. (800) 421-3756.

October 15-17—**11th Annual Seminar: Cardiology Update 1987.** American College of Cardiology at Quail Lodge, Carmel. Thurs-Sat. Contact: Mary Anne McInerny, ACC, 9111 Old Georgetown Rd, Bethesda, MD 20814. (301) 897-5400.

October 30-31—**Coronary Heart Disease.** Medical Education Resources at Las Vegas Hilton Hotel, Nevada. Fri-Sat. 11 hrs. $295. Contact: Medical Education Resources, 5808 S Rapp St, Ste 202, Littleton, CO 80120. (800) 421-3756.

## DERMATOLOGY

June 5-6—**6th Annual Southwestern Regional Cutaneous Flap Workshop.** UCLA at UCLA. Fri-Sat. 11 hrs. Contact: UCLA.

August 13-15—**Problems of the Aging Skin.** STAN at Hyatt Rickeys Hotel, Palo Alto. Thurs-Sat. Contact: STAN.

August 14-15—**Cryostat and Microscopically Controlled Surgical Workshop.** UCSD. Fri-Sat. 15 hrs. Contact: Daniel E. Gormley, MD, Director, 412 W Carroll, Glendora 91740. (818) 963-7684.

October 24-25—**16th Annual Mycology Review.** STAN at STAN. Sat-Sun. Contact: STAN.

## EMERGENCY MEDICINE

May 15-17—**Update in Cardiology/Resuscitation.** Superior California Medical Education Council, Redding at Alexander Valley (cycling tour). Fri-Sun. 6 hrs. Contact: J. Bear Co, PO Box 117, Burney 96013. (916) 335-3388.

June 1-5—**Topics in Emergency Medicine.** UCSF at Holiday Inn Union Square, San Francisco. Mon-Fri. 31 hrs. $420. Contact: UCSF.

June 11-12—**Occupational and Environmental Medicine.** UCD at Capitol Plaza Holiday Inn, Sacramento. Thurs-Fri. 7 hrs. Contact: UCD.

June 22-26—**Postgraduate Institute for Emergency and Primary Care Physicians, Symposium III and Advanced Emergency Procedures Lab.** UCSD at Hanalei Hotel, San Diego. Mon-Fri. 32 hrs. $325-440. Contact: UCSD.

June 25-28—**Wilderness Emergency Care.** Superior California Medical Education Council at Lava Creek Fishing Lodge, Fall River Mills. Thurs-Sun. 6 hrs. Contact: J. Bear Co, PO Box 117, Burney 96013. (916) 335-3388.

July 24-26—**Advanced Cardiac Life Support.** CPR Seminars at Ralph K. Davies Medical Center. San Franicsco. Fri-Sun. Contact: CPR Seminars, 833 Market St, Ste 421, San Francisco 94103. (415) 543-7282.

August 12-16—**Wilderness Medicine: 1987.** Siskiyou General Hospital at Northstar, Tahoe Resort. Wed-Sun. 20 hrs. $395. Contact: Jackie Silva, PO Box 321, Yreka 96097. (916) 842-6848.

August 17-21—**Postgraduate Institute for Emergency and Primary Care Physicians, Symposium II and Advanced Emergency Procedures Lab.** UCSD at UCSD. Mon-Fri. 32 hrs. $325-440. Contact: UCSD.

August 23-28—**New Advances in Internal Medicine.** UCD at Hyatt Monterey. Sun-Fri. Contact: UCD.

October 16-17—**2nd Annual Symposium on Advanced Pediatric Emergency Medicine and Trauma.** UCI at Long Beach Airport Marriott Hotel. Fri-Sat. Contact: UCI.

October 23-25—**Advanced Cardiac Life Support.** CPR Seminars at Ralph K. Davies Medical Center, San Francisco. Fri-Sun. Contact: CPR Seminars, 833 Market St, Ste 421, San Francisco 94103. (415) 543-7282.

## INTERNAL MEDICINE

May 16—**Clinical Aspects of Viral Disease.** Grossmont District Hospital at Kona Kai Club, San Diego. Sat. Contact: Vera Belyeu, Grossmont District Hospital, 5555 Grossmont Center Dr, La Mesa 92041. (619) 465-0711, ext 245.

May 18-22—**Advances in Internal Medicine.** UCSF at Hyatt on Union Square, San Francisco. Mon-Fri. 32 hrs. $440. Contact: UCSF.

May 19-20—**Laboratory Diagnosis in Clinical Practice: Advances in Clinical Laboratory Testing.** Tues-Wed. 11 hrs. $225. Contact: UCSF.

June 17-19—**Gastroenterology: Recent Developments in Theory and Practice.** UCSF at Hyatt on Union Square, San Francisco. Wed-Fri. 17 hrs. $375. Contact: UCSF.

June 22-26—**Advances in Internal Medicine.** UCSF at UCSF. Mon-Fri. 32 hrs. $440.

June 26—**Mucosal Injury, Esophageal Dysfunction, and Sleep Disorders.** Sequoia Hospital District, Redwood City. Fri. 7 hrs. $110. Contact: Daniel Liebowitz, MD, Sequoia Hospital, Whipple and Alameda, Redwood City 94062. (800) 345-0409.

July 18-20—**8th Annual Symposium on Laboratory and Clinical Aspects of Microbiological Diagnosis.** UCLA at Hyatt Regency Hotel, Monterey. Sat-Mon. 13 hrs. $175. Contact: UCLA.

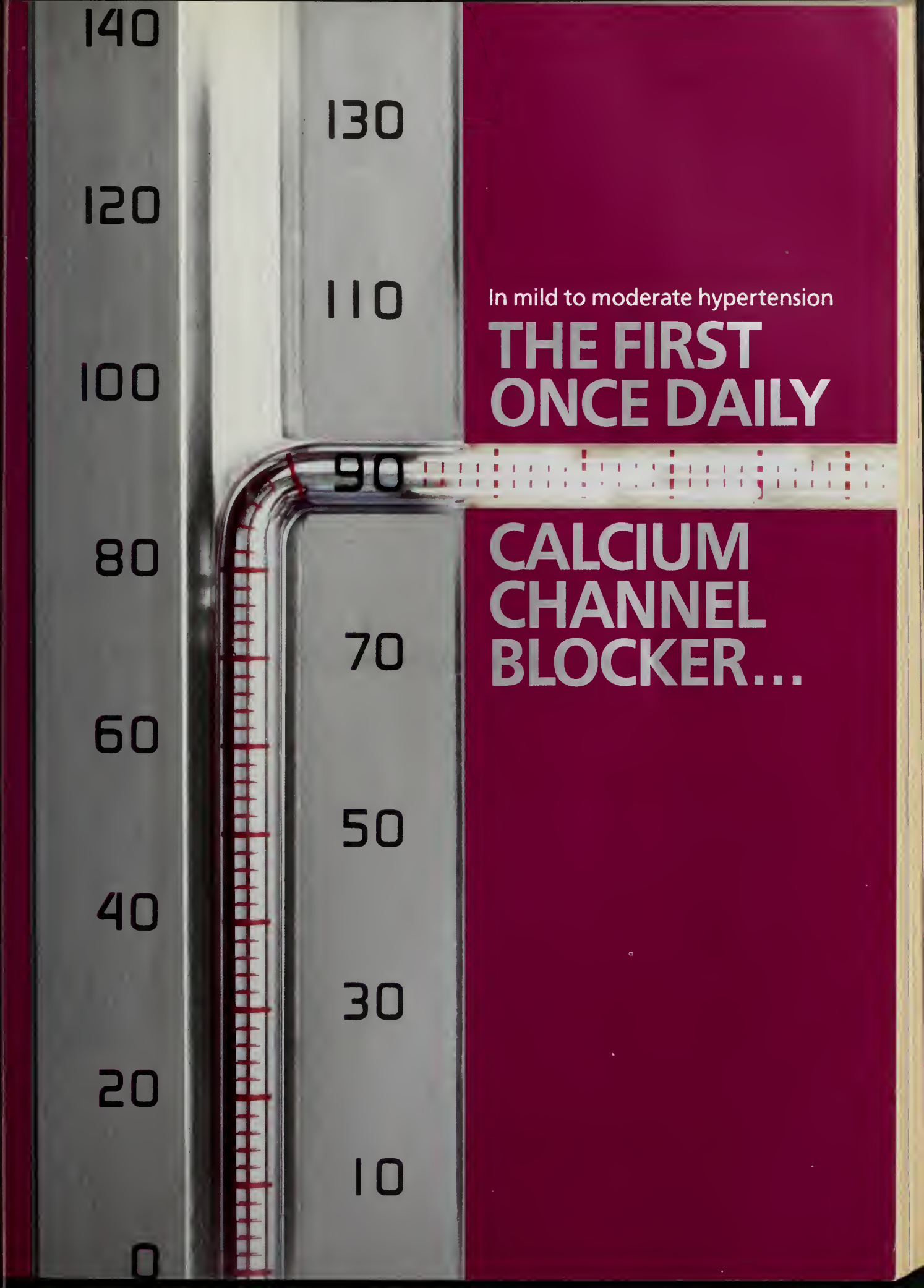
## OB/GYN

June 5-7—**OB/GYN: Antepartum and Intrapartum Management.** UCSF at Hyatt on Union Square, San Francisco. Fri-Sun. 18 hrs. $200-320. Contact: UCSF.

June 11-13—**Gynecologic Oncology and Breast Disease.** American College of Obstetricians and Gynecologists at Fairmont Hotel, San Francisco. Thurs-Sat. Contact: Robin Murray, ACOG, 600 Maryland Ave, SW, Washington, DC 20024-2588. (202) 638-5577.

June 25-26—**Advanced Fetal Heart Rate Monitoring.** UCI at Balboa Bay Club, Newport Beach. Thurs-Fri. 12 hrs. Contact: UCI.

(Continued on Page 563)




In mild to moderate hypertension

# THE FIRST ONCE DAILY CALCIUM CHANNEL BLOCKER...

**NEW**
ONCE DAILY

# ISOPTIN SR*

## (verapamil HCl/Knoll)

*240 mg scored, sustained-release tablets*

**JAMES B.**
38, black male, heavy smoker. Prescribed a diuretic by another physician last year for hypertension.

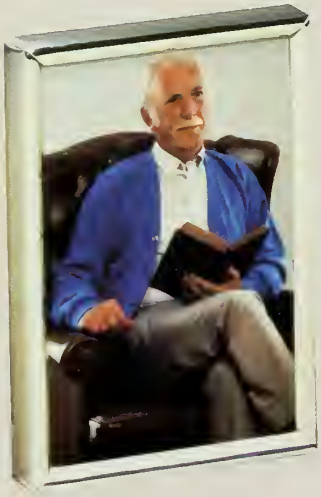
**YOUR CONCERNS**
Presents with "smoker's cough." Workup reveals a BP of 150/107.

**A LOGICAL CHOICE FOR CONTROL OF HIS BP**
ISOPTIN* (verapamil HCl/Knoll) because...
— Black hypertensives often have low plasma renin activity and generally do not respond favorably to beta blockers.
— Beta blockers may increase the likelihood of bronchospasm.

**ALICE W.**
65, diabetic, overweight. Her BP has elevated to 190/98.

**YOUR CONCERNS**
She's on daily insulin.

**A LOGICAL CHOICE FOR CONTROL OF HER BP**
ISOPTIN* (verapamil HCl/Knoll) because...
— Unlike most beta blockers and diuretics, ISOPTIN has no adverse effects on serum glucose levels.
— Unlike most beta blockers, ISOPTIN does not mask the symptoms of hypoglycemia.



**THOMAS G.**
70, asthmatic. In the past, BP adequately controlled with 25 mg hydrochlorothiazide daily.

**YOUR CONCERNS**
Today patient presents with symptoms of gout. Workup reveals high uric acid level, low serum potassium, and BP elevated to 180/98.

**A LOGICAL CHOICE FOR CONTROL OF HIS BP**
ISOPTIN* (verapamil HCl/Knoll) because...
— Unlike diuretics, ISOPTIN will not decrease serum potassium levels or elevate uric acid levels.
— Unlike beta blockers, ISOPTIN can be used safely in asthma and COPD patients.

**JOHN K.**
42, Annual physical uncovered diastolic BP of 102... confirmed on three successive office visits. Unresponsive to nonpharmacologic intervention.

**YOUR CONCERNS**
Salesman, spends many hours of his working day in car... total cholesterol level 300, HDL 35.

**A LOGICAL CHOICE FOR CONTROL OF HIS BP**
ISOPTIN* (verapamil HCl/Knoll) because...
— Unlike diuretics, ISOPTIN does not cause urinary urgency.
— Unlike either beta blockers or diuretics, ISOPTIN will not adversely affect his already seriously compromised lipid profile.
— Unlike with propranolol, fatigue and impotence are rarely reported.

## *Antihypertensive therapy you and your patients can live with*

*A product of Knoll research.

© 1986, BASF K & F Corporation

2538/2-87

Knoll Pharmaceuticals
A Unit of BASF K&F Corporation
Whippany, New Jersey 07981

BASF Group

knoll®

Printed in U.S.A.

Please see adjacent page for brief summary.

*In mild to moderate hypertension* Brief Summary

***THE FIRST ONCE DAILY CALCIUM CHANNEL BLOCKER***

**ISOPTIN® SR (verapamil HCl/Knoll) 240 mg scored, sustained-release tablets**

**CONTRAINOICATIONS:** 1) Severe left ventricular dysfunction (see WARNINGS), 2) Hypotension (less than 90 mmHg systolic pressure) or cardiogenic shock, 3) Sick sinus syndrome or 2nd or 3rd degree AV block (except in patients with a functioning artificial ventricular pacemaker).

**WARNINGS: Heart Failure:** ISOPTIN should be avoided in patients with severe left ventricular dysfunction (see DRUG INTERACTIONS). Patients with milder ventricular dysfunction should, if possible, be controlled before verapamil treatment. Hypotension: ISOPTIN (verapamil HCl) may produce occasional symptomatic hypotension. Elevated Liver Enzymes: Elevations of transaminases with and without concomitant elevations in alkaline phosphatase and bilirubin have been reported. Periodic monitoring of liver function in patients receiving verapamil is therefore prudent. Accessory Bypass Tract (Wolff-Parkinson-White): Patients with paroxysmal and/or chronic atrial flutter or atrial fibrillation and a coexisting accessory AV pathway have developed increased antegrade conduction across the accessory pathway producing a very rapid ventricular response or ventricular fibrillation after receiving intravenous verapamil. While this has not been reported with oral verapamil, it should be considered a potential risk. Treatment is usually D.C.-cardioversion. Atrioventricular Block: The effect of verapamil on AV conduction and the SA node may cause asymptomatic 1st degree AV block and transient bradycardia. Higher degrees of AV block, while infrequent (0.8%), may require a reduction in dosage or, in rare instances, discontinuation of verapamil HCl. Patients with Hypertrophic Cardiomyopathy (IHSS): Although verapamil has been used in the therapy of patients with IHSS, severe cardiovascular decompensation and death have been noted in this patient population.

**PRECAUTIONS: Impaired Hepatic or Renal Function:** Verapamil is highly metabolized by the liver with about 70% of an administered dose excreted in the urine. In patients with impaired hepatic or renal function verapamil should be administered cautiously and the patients monitored for abnormal prolongation of the PR interval or other signs of excessive pharmacological effects (see OVERDOSAGE).

**Drug Interactions:** Beta Blockers: Concomitant use of ISOPTIN and oral beta-adrenergic blocking agents may be beneficial in certain patients with chronic stable angina or hypertension, but available information is not sufficient to predict with confidence the effects of concurrent treatment in patients with left ventricular dysfunction or cardiac conduction abnormalities. Digitalis: Clinical use of verapamil in digitalized patients has shown the combination to be well tolerated if digoxin doses are properly adjusted. However, chronic verapamil treatment increases serum digoxin levels by 50 to 75% during the first week of therapy and this can result in digitalis toxicity. Upon discontinuation of ISOPTIN (verapamil HCl), the patient should be reassessed to avoid underdigitalization. Antihypertensive Agents: Verapamil administered concomitantly with oral antihypertensive agents (e.g., vasodilators, angiotensin-converting enzyme inhibitors, diuretics, beta blockers, prazosin) will usually have an additive effect on lowering blood pressure. Patients receiving these combinations should be appropriately monitored. Disopyramide: Disopyramide should not be administered within 48 hours before or 24 hours after verapamil administration. Quinidine: In patients with hypertrophic cardiomyopathy (IHSS), concomitant use of verapamil and quinidine resulted in significant hypotension. There has been a report of increased quinidine levels during verapamil therapy. Nitrates: The pharmacologic profile of verapamil and nitrates as well as clinical experience suggest beneficial interactions. Cimetidine: Two clinical trials have shown a lack of significant verapamil interaction with cimetidine. A third study showed cimetidine reduced verapamil clearance and increased elimination to 1/2. Anesthetic Agents: Verapamil may potentiate the activity of neuromuscular blocking agents and inhalation anesthetics. Carbamazepine: Verapamil may increase carbamazepine concentrations during combined therapy. Rifampin: Therapy with rifampin may markedly reduce oral verapamil bioavailability. Lithium: Verapamil may lower lithium levels in patient on chronic oral lithium therapy. Carcinogenesis, Mutagenesis, Impairment of Fertility: There was no evidence of a carcinogenic potential of verapamil administered to rats for two years. Verapamil was not mutagenic in the Ames test. Studies in female rats did not show impaired fertility. Effects on male fertility have not been determined. Pregnancy (Category C): There are no adequate and well-controlled studies in pregnant women. ISOPTIN crosses the placental barrier and can be detected in umbilical vein blood at delivery. This drug should be used during pregnancy, labor, and delivery, only if clearly needed. Nursing Mothers: ISOPTIN is excreted in human milk, therefore, nursing should be discontinued while verapamil is administered. Pediatric Use: Safety and efficacy of ISOPTIN in children below the age of 18 years have not been established.

**ADVERSE REACTIONS:** Constipation 8.4%, dizziness 3.5%, nausea 2.7%, hypotension 2.5%, edema 2.1%, headache 1.9%, CHF/pulmonary edema 1.8%, fatigue 1.7%, bradycardia 1.4%, 3° AV block 0.8%, flushing 0.1%, elevated liver enzymes (see WARNINGS). The following reactions, reported in less than 1.0% of patients, occurred under conditions (open trials, marketing experience) where a causal relationship is uncertain; they are mentioned to alert the physician to a possible relationship: angina pectoris, arthralgia and rash, AV block, blurred vision, cerebrovascular accident, chest pain, claudication, confusion, diarrhea, dry mouth, dyspnea, ecchymosis or bruising, equilibrium disorders, exanthema, gastrointestinal distress, gingival hyperplasia, gynecomastia, hair loss, hyperkeratosis, impotence, increased urination, insomnia, macules, muscle cramps, myocardial infarction, palpitations, paresthesia, psychotic symptoms, purpura (vasculitis), shakiness, somnolence, spotty menstruation, sweating, syncope, urticaria. Treatment of Acute Cardiovascular Adverse Reactions: Whenever severe hypotension or complete AV block occur following oral administration of verapamil, the appropriate emergency measures should be applied immediately, e.g., intravenously administered isoproterenol HCl, levarterenol bitartrate, atropine (all in the usual doses), or calcium gluconate (10% solution). If further support is necessary, inotropic agents (dopamine or dobutamine) may be administered. Actual treatment and dosage should depend on the severity and the clinical situation and the judgment and experience of the treating physician.

**OVEROOSAGE:** Treatment of overdosage should be supportive. Beta-adrenergic stimulation or parenteral administration of calcium solutions may increase calcium ion flux across the slow channel, and have been used effectively in treatment of deliberate overdosage with verapamil. Clinically significant hypotensive reactions or fixed high degree AV block should be treated with vasopressor agents or cardiac pacing, respectively. Asystole should be handled by the usual measures including cardiopulmonary resuscitation.

**Knoll Pharmaceuticals**
A Unit of BASF K&F Corporation
Whippany, New Jersey 07981

**BASF** Group

knoll®

©1986, BASF K&F Corporation 2474/11/86 Printed in U.S.A.



## CONTINUING MEDICAL EDUCATION

*(Continued from Page 562)*

June 30-July 5—**5th Annual Controversies in Obstetrics and Gynecology.** UCI at Mauna Kea Beach Resort, Hawaii. Tues-Sun. 22 hrs. Contact: UCI.

July 16-18—**Developmental Interventions in Neonatal Care.** American Academy of Pediatrics at San Francisco. Thurs-Sat. 17 hrs. Contact: Contemporary Forums, 530 La Gonda Way, Ste E, Danville 94526. (415) 820-2800.

October 16-18—**Advanced Fetal Heart Rate Monitoring.** UCI at Embassy Suites Hotel, Napa Valley. Fri-Sun. Contact: UCI.

### OPHTHALMOLOGY

August 1-8—**Ophthalmology.** USC at Mauna Kea, Hawaii. One week. 26 hrs. $525. Contact: USC.

August 30-Sept 2—**Under Pressure: Glaucoma 1987.** UCD at Hyatt Lake Tahoe, Incline Village, Nevada. Sun-Wed. Contact: UCD.

### ORTHOPEDICS

June 14-19—**Fingers to the Toes: Orthopaedics for Primary Care.** UCD at Stanford Sierra Camp, Fallen Leaf Lake. Sun-Fri. Contact: UCD.

### PATHOLOGY

May 21-22—**Annual Meeting: Current Issues in Anatomic Pathology.** UCSF at San Francisco. Thurs-Fri. 12 hrs. Contact: UCSF.

May 23—**Fine Needle Aspiration Tutorial.** UCSF at UCSF. Sat. 7 hrs. $475. Contact: UCSF.

August 22-29—**7th Annual Symposium on Fine Needle Aspiration.** California Society of Pathologists and UCSF at Royal Lahaina Resort, Kaanapali Beach, Maui, Hawaii. One week. 24.5 hrs. Contact: UCSF.

October 3—**Fine Needle Aspiration Tutorial.** UCSF at UCSF. Sat. 7 hrs. $475. Contact: UCSF.

### PEDIATRICS

May 23-25—**Annual Spring Seminar.** American Academy of Pediatrics at Hyatt Regency Hotel, Monterey. Sat-Mon. Contact: AAP, PO Box 1297, Orange 92668. (714) 978-2415.

July 24-25—**Debates and Updates in Pediatric Emergencies.** UCSF at Hyatt on Union Square, San Francisco. Fri-Sat. 14 hrs. $235. Contact: UCSF.

September 12-13—**44th Annual Brennemann Memorial Lectures.** Los Angeles Pediatric Society at Sheraton Universal Hotel, Los Angeles. Sat-Sun. Contact: Los Angeles Pediatric Society, PO Box 9022, Inglewood 90305. (213) 757-1198.

October 10-17—**11th Annual Pediatrics for the Practitioner.** UCI at Mauna Kea Beach, Hawaii. One week. Contact: UCI.

October 16-17—**2nd Annual Symposium on Advanced Pediatric Emergency Medicine and Trauma.** UCI at Long Beach Airport Marriott Hotel. Fri-Sat. Contact: UCI.

October 16-18—**Current Advances in Pediatrics.** American Academy of Pediatrics and UCI at Disneyland Hotel, Anaheim. Fri-Sun. Contact: AAP, PO Box 1297, Orange 92668. (714) 978-2415.

October 23-25—**Current Concepts in Pediatric Gastroenterology.** Children's Hospital, Oakland at Doubletree Hotel, Monerey. Fri-Sun. Contact: Kim Leadon, CME Office, Children's Hospital, 747 52nd St, Oakland 94609. (415) 428-3021.

### PSYCHIATRY

October 17-18—**Dynamics of Human Development—Implications for Treatment.** Continuing Education Seminars at Los Angeles. Sat-Sun. 11.5 hrs. $175. Contact: Continuing Education Seminars, 1023 Westholme Ave, Los Angeles 90024. (213) 475-8300.

*(Continued on Page 642)*

(Continued from Page 550)

622 **The Role of Irradiation**
B. SHARON COLE, MD
FRANCIS M. FILLOUX, MD, and JEANNETTE J. TOWNSEND, MD, Reply

622 **Incidence of Cough Associated With Captopril Therapy**
GERALD R. DRESLINSKI, MD

## TOPICS IN PRIMARY CARE MEDICINE

623 **Urinary Incontinence**
MAJ KURT KROENKE, MC, USA, and CAPT G. DOUGLAS CORRIE, MC, USA
*From the General Medicine Service, Department of Medicine, and the Urology Service, Department of Surgery, Brooke Army Medical Center, Fort Sam Houston, Texas.*

## HEALTH CARE DELIVERY

627 **Survival Following Cardiac Transplantation—What Are Acceptable Standards?**
DALE G. RENLUND, MD; MICHAEL R. BRISTOW, MD, PhD; NELSON A. BURTON, MD; KENT W. JONES, MD; S. V. KARWANDE, MD, and WILLIAM A. GAY, Jr, MD
*From the Utah Cardiac Transplant Program, Division of Cardiology, University of Utah School of Medicine Medical Center, the Veterans Administration Medical Center and the Latter-Day Saints Hospital, Salt Lake City.*

## PUBLIC HEALTH AND PREVENTIVE MEDICINE

631 **Preventive Dentistry Update—Dental Sealants**
ROBERT ISMAN, DDS, MPH, and KENNETH W. KIZER, MD, MPH
*From the Office of Dental Health, California Department of Health Services, Sacramento.*

## MEDICAL ETHICS

633 **Consultations in Clinical Ethics—Issues and Questions in 27 Cases**
JOHN LA PUMA, MD
*From the Center for Clinical Medical Ethics, Division of Biological Sciences, University of Chicago, and the Department of Medicine, The Pritzker School of Medicine, Chicago.*

## INFORMED OPINION

638 **Physicians and the Death Penalty**
KIM MARIE THORBURN, MD
*From the Department of Medicine, University of Hawaii John A. Burns School of Medicine, Honolulu.*

## OTHER FEATURES

552 **Books Received**

558 **Subscription Information**

560 **Continuing Medical Education Activities in Arizona; California, Hawaii and Nevada; Idaho; Montana; New Mexico; Utah; Washington; Wyoming**

643 **Idaho Medical Association Annual Meeting**

647 **Classified Advertising**

653 **Arizona Medical Association Annual Meeting**

655 **Wyoming Medical Society Annual Meeting**

657 **Western State Medical Associations' Meetings**

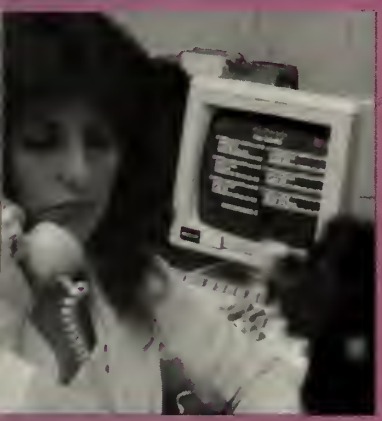
★ **Official Journal of the Arizona Medical Association, the California Medical Association, the Idaho Medical Association, the Montana Medical Association, the Nevada State Medical Association, the New Mexico Medical Society, the Utah State Medical Association, the Washington State Medical Association and the Wyoming Medical Society. Affiliated Specialty Society: California Society of Internal Medicine.**

★ **Affiliated Clinical Investigation Societies: the Western Association of Physicians; the Western Society for Clinical Investigation; the Western Section, American Federation for Clinical Research; the Western Society for Pediatric Research; the Western Region, Society for Investigative Dermatology.**

## chnology

E RESIDENT" is a compre-
sive medical office computer
em designed to meet the
plex needs of today's
ical office.

rograms in "THE RESIDENT"
accessed through menus.
rations are smooth and
. Patient record access can
y name, partial name, or
e-defined code. Mainten-
tables (RVS, ICD-9, Insur-
Company, etc.) may be set
sing existing codes com-
to the particular office.



rations may be temporarily
ended, a new task per-
ied, and then resume the
nal task at the exact place
re operation was sus-
ded. This feature is useful
dding a new insurance
pany without having to skip
ugh numerous screens.

software was designed for
p practices, but performs
lly as well in a busy solo
tice.

## pport Service

ver 7 years, SYZYGY has
ided such services as: com-
r installations, cabling,
training, management con-
ng, and hardware/software
ort.

# SYZYGY

## Key Features

- *Latest industry-accepted software technology*
- *Protection against software obsolescence*
- *Modular software application packages*
- *Multi-user/multi-terminals/multi-office*
- *Three tiered self-help capability*
- *Office defined practice policies*
- *No codes to remember*
- *Suspend an operation, jump to a new task, and return*
- *Bridge between database and word processor*

## Modular Software

With Wallaby's modular software, there is never a need to purchase and implement more capability than you need. You buy only what you require. Each software configuration, however, is complete of itself...there are no costly options to any module to fill the needs of a particular medical speciality. For example:

- *Patient Billing*
- *Accounts Receivable*
- *Practice Analysis*
- *Insurance Forms Formatter*
- *Appointment Scheduling*
- *Report Generator*
- *Electronic Forms Submission*
- *Word Processing*
- *General Ledger*
- *Accounts Payable*
- *Payroll*
- *Supply Inventory*
- *Telecommunications*

## Expandability

Expansion can take place at any time...the user may add terminals and printers, increase the storage capacity, and install additional software modules without modification of existing operational procedures. This Medical Practice Management System grows to match your needs.

Y Z Y G Y®
mputer Systems, Inc.
Borrego Court, San Dimas, CA 91773

*FOR MORE INFORMATION PLEASE CALL*

(800) 824-0532
(818) 332-3320

# Motrin® 800 TABLETS mg

ibuprofen

## a stronger reason to prescribe Motrin Tablets

©1986 The Upjohn Company

# Motrin® 800 TABLETS mg

ibuprofen

## Extra-Strength Motrin Tablets— a convenient way to tap the full potential of Motrin:

**The newest strength of *Motrin* Tablets**

**makes treatment easier** for arthritis patients who need the doses that provide higher levels of anti-inflammatory activity as well as potent analgesia...just 1 tablet t.i.d. provides 2400 mg/day.

**expands the dosage convenience** of MOTRIN Tablets – makes it even easier to adjust the dosage of MOTRIN to each patient's needs...the dosage range of up to 3200 mg/day can be achieved on a q.i.d. regimen. Gastroscopic studies at varying doses show an increased tendency toward gastric irritation at higher doses. However, at comparable doses, gastric irritation is about half that seen with aspirin.

**provides economy...** patients should pay less for MOTRIN Tablets than for comparable dosages of sulindac, piroxicam, or naproxen.

**provides, above all, the experience-proven efficacy and safety profile of *Motrin.*** MOTRIN continues to be America's most often prescribed nonsteroidal anti-inflammatory agent.

Please see adjacent page for a brief summary of prescribing information.

Upjohn 100 A Century of Caring 1886·1986

**MOTRIN® Tablets**
(ibuprofen)

**CONTRAINDICATIONS:** Anaphylactoid reactions have occurred in individuals hypersensitive to MOTRIN or with the syndrome of nasal polyps, angioedema and bronchospastic reactivity to aspirin or other nonsteroidal anti-inflammatory agents.

**WARNINGS:** Peptic ulceration and G.I. bleeding, sometimes severe, have been reported. Ulceration, perforation and bleeding may end fatally. An association has not been established. Use MOTRIN under close supervision in patients with a history of upper gastrointestinal tract disease, after consulting ADVERSE REACTIONS. In patients with active peptic ulcer and active rheumatoid arthritis, try nonulcerogenic drugs, such as gold. If MOTRIN is used, observe the patient closely for signs of ulcer perforation or G.I. bleeding.

**PRECAUTIONS:** Blurred and/or diminished vision, scotomata, and/or changes in color vision have been reported. If these develop, discontinue MOTRIN and the patient should have an ophthalmologic examination, including central visual fields and color vision testing.

Fluid retention and edema have been associated with MOTRIN; use with caution in patients with a history of cardiac decompensation or hypertension.

MOTRIN can inhibit platelet aggregation and prolong bleeding time. Use with caution in persons with intrinsic coagulation defects and on anticoagulant therapy.

Patients should report signs or symptoms of gastrointestinal ulceration or bleeding, blurred vision, skin rash, weight gain, or edema.

Patients on prolonged corticosteroid therapy should have therapy tapered slowly when MOTRIN is added.

The antipyretic, anti-inflammatory activity of MOTRIN may mask inflammation and fever.

As with other nonsteroidal anti-inflammatory drugs, borderline elevations of liver tests may occur in up to 15% of patients. These abnormalities may progress, may remain essentially unchanged, or may be transient with continued therapy. Meaningful elevations of SGPT or SGOT (AST) occurred in controlled clinical trials in less than 1% of patients. Severe hepatic reactions, including jaundice and cases of fatal hepatitis, have been reported with ibuprofen as with other nonsteroidal anti-inflammatory drugs. If liver disease develops or if systemic manifestations occur (e.g. eosinophilia, rash, etc.), MOTRIN should be discontinued.

In cross-study comparisons with 1200 mg to 3200 mg daily for several weeks, a slight dose-response decrease in hemoglobin/hematocrit was noted. The total decrease in hemoglobin usually does not exceed 1 gram.

**Renal Effects:** Long term administration of ibuprofen and other NSAID's to animals has resulted in renal papillary necrosis and other abnormal renal pathology. In humans, there have been reports of acute interstitial nephritis with hematuria, proteinuria, and occasionally nephrotic syndrome. In patients with prerenal conditions and reduced renal blood flow or blood volume, NSAID's may precipitate overt renal decompensation. Patients with impaired renal function, heart failure, liver dysfunction, those taking diuretics and the elderly are at greatest risk. Discontinuation of NSAID therapy is typically followed by recovery to the pretreatment state.

In patients with renal impairment, reduced dosage may be necessary. Prospective studies of MOTRIN safety in patients with chronic renal failure have not been done.

**Drug Interactions: Aspirin:** Used concomitantly may decrease MOTRIN blood levels.

**Coumarin:** Bleeding has been reported in patients taking MOTRIN and coumarin.

**Pregnancy and nursing mothers:** MOTRIN should not be taken during pregnancy or by nursing mothers.

**ADVERSE REACTIONS:** The most frequent type of adverse reaction occurring with MOTRIN is gastrointestinal of which one or more occurred in 4% to 16% of the patients. Reported side effects were higher at 3200 than at 2400 mg/day or less.

***Incidence Greater than 1% (but less than 3%) – Probable Causal Relationship***

**GASTROINTESTINAL:** Nausea,* epigastric pain,* heartburn,* diarrhea, abdominal distress, nausea and vomiting, indigestion, constipation, abdominal cramps or pain, fullness of GI tract (bloating and flatulence); **CENTRAL NERVOUS SYSTEM:** Oizziness,* headache, nervousness; **DERMATOLOGIC:** Rash* (including maculopapular type), pruritus; **SPECIAL SENSES:** Tinnitus; **METABOLIC/ENDOCRINE:** Oecreased appetite; **CARDIOVASCULAR:** Edema, fluid retention (generally responds promptly to drug discontinuation; see PRECAUTIONS).

***Incidence less than 1% Probable Causal Relationship****

**GASTROINTESTINAL:** Gastric or duodenal ulcer with bleeding and/or perforation, gastrointestinal hemorrhage, melena, gastritis, hepatitis, jaundice, abnormal liver function tests; **CENTRAL NERVOUS SYSTEM:** Oepression, insomnia, confusion, emotional lability, somnolence, aseptic meningitis with fever and coma; **DERMATOLOGIC:** Vesiculobullous eruptions, urticaria, erythema multiforme, Stevens-Johnson syndrome, alopecia; **SPECIAL SENSES:** Hearing loss, amblyopia (blurred and/or diminished vision, scotomata and/or changes in color vision) (see PRECAUTIONS); **HEMATOLOGIC:** Neutropenia, agranulocytosis, aplastic anemia, hemolytic anemia (sometimes Coombs positive), thrombocytopenia with or without purpura, eosinophilia, decreases in hemoglobin and hematocrit (see PRECAUTIONS); **CARDIOVASCULAR:** Congestive heart failure in patients with marginal cardiac function, elevated blood pressure, palpitations; **ALLERGIC:** Syndrome of abdominal pain, fever, chills, nausea and vomiting; anaphylaxis, bronchospasm (see CONTRAINOICATIONS); **RENAL:** Acute renal failure in patients with pre-existing significantly impaired renal function, decreased creatinine clearance, polyuria, azotemia, cystitis, hematuria; **MISCELLANEOUS:** Ory eyes and mouth, gingival ulcer, rhinitis.

***Incidence less than 1% – Causal Relationship Unknown****

**GASTROINTESTINAL:** Pancreatitis; **CENTRAL NERVOUS SYSTEM:** Paresthesias, hallucinations, dream abnormalities, pseudotumor cerebri; **DERMATOLOGIC:** Toxic epidermal necrolysis, photoallergic skin reactions; **SPECIAL SENSES:** Conjunctivitis, diplopia, optic neuritis, cataracts; **HEMATOLOGIC:** Bleeding episodes (e.g epistaxis, menorrhagia); **METABOLIC/ENDOCRINE:** Gynecomastia, hypoglycemic reaction, acidosis; **CARDIOVASCULAR:** Arrhythmias (sinus tachycardia, sinus bradycardia); **ALLERGIC:** Serum sickness, lupus erythematosus syndrome, Henoch-Schonlein vasculitis, angioedema; **RENAL:** Renal papillary necrosis.

*Reactions occurring in 3% to 9% of patients treated with MOTRIN. (Those reactions occurring in less than 3% of the patients are unmarked).

**Reactions are classified under **"Probable Causal Relationship (PCR)"** if there has been one positive rechallenge or if three or more cases occur which might be causally related. Reactions are classified under **"Causal Relationship Unknown"** if seven or more events have been reported but the criteria for PCR have not been met.

**OVERDDSAGE:** In cases of acute overdosage, the stomach should be emptied. The drug is acidic and excreted in the urine so alkaline diuresis may be beneficial.

**DDSAGE AND ADMINISTRATION:** Oo not exceed 3200 mg/day.

Rheumatoid and osteoarthritis: Suggested dosage is 1200 to 3200 mg per day (400, 600 or 800 mg t.i.d. or q.i.d.). The smallest effective dosage should be used. Mild to moderate pain: 400 mg every 4 to 6 hours as necessary.

**HOW SUPPLIED:**

| MOTRIN Tablets, 400 mg (orange) | MOTRIN Tablets, 600 mg (peach) | MOTRIN Tablets, 800 mg (apricot) |
|---|---|---|
| Bottles of 500 | Bottles of 500 | Bottles of 100 |
| Unit-dose package of 100 | Unit-dose package of 100 | Bottles of 500 |
| Unit of Use bottles of 100 | Unit of Use bottles of 100 | |

**CAUTIDN:** FEDERAL LAW PROHIBITS OISPENSING WITHOUT PRESCRIPTION.

**For additional product information, see your Upjohn representative or consult the package insert.**

MED B-9-S

Upjohn 100 A Century of Caring 1886·1986

February 1986
J-6321

# ROCKY MOUNTAIN RURAL TRAUMA SYMPOSIUM

## Montana State University Bozeman, Montana August 3-5, 1987

## The Symposium

The Rocky Mountain Rural Trauma Symposium is the first trauma symposium designed to address the unique needs of physicians and nurses practicing in rural areas. An outstanding visiting faculty of trauma specialists is teamed with the finest Montana physicians and nurses to assure a consistent rural focus in the workshops and meetings. The goal of this symposium is to provide professionals who face severe trauma infrequently in environments where resources are limited with the most current knowledge of trauma care as well as practical application in the rural setting.

### Credits

Montana State University has approved this symposium for 17 CEUs. Application has been made to all appropriate CME providers.

### Sponsors

AHEC-A Regional Partner of the University of Washington School of Medicine; Montana State University; Montana Committee on Trauma; Montana EMS Bureau.

### Offered in Cooperation With

The Departments of Surgery
University of Washington School of Medicine
Oregon Health Sciences University

### For More Information and Program

Contact Continuing Education for the Health Professional, 303 Montana Hall, Montana State University, Bozeman, MT 59717.

### FEES

**$350 for physicians, $180 for nurses.**

## THE PROBLEM

Most physicians today are falling short of their personal financial goals. Competitive pressures from a growing number of providers and from aggressive HMO's have resulted in a decline in the average physician net income.

Economic survival in today's medical market requires more than the ability to practice good medicine. You also need to practice the sound management of your financial resources and business office, topics rarely discussed in medical school.

So if you're not satisfied with your cash flow or net revenue, read on . . .

## THE SOLUTION

Medical Office Consultants will make a detailed evaluation of your office financial and marketing systems. Depending upon your specific needs, a complete range of services can be provided, including a team who trains your staff, monitors office procedures and implements proven practice management and marketing techniques.

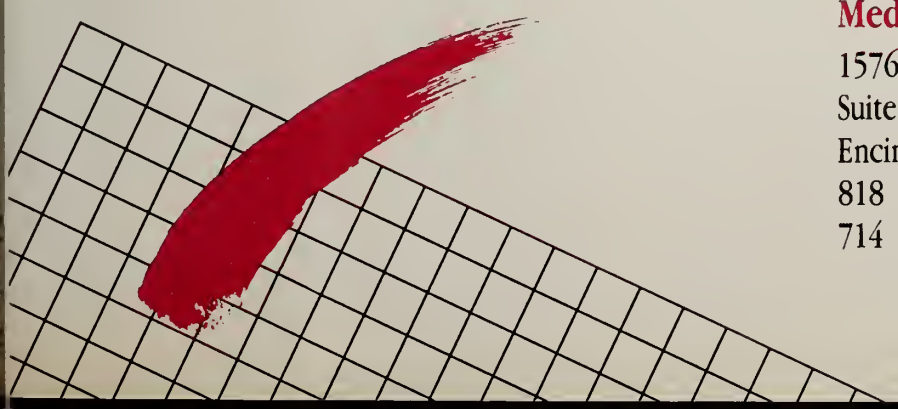
An abbreviated list of our services includes the following:

- Review, recommend and implement accounting, billing, collections and purchasing procedures to enhance cash flow and overall efficiency in the business office.
- Develop internal and external marketing strategies to both generate and retain patients.
- Design a wide range of personal financial plans and strategies to minimize tax liabilities and investment risk, and maximize personal income and satisfaction.

## THE COMPANY

Medical Office Consultants is a group of professionals with extensive background in medical office management, accounting, banking, legal, health care marketing, insurance and real estate. We would like to demonstrate to you our ability to problem solve, identify opportunities and implement strategies benefiting your practice and you, personally.

So if you're not realizing your financial expectations, act now!



**Medical Office Consultants**
15760 Ventura Boulevard
Suite 1206
Encino, California 91436
818 / 906-3630
714 / 632-7212

# A better alternative for hypertensives who are going bananas...

Spare your patients the extra cost—in calories, sodium and dollars.

Spare your patients the rigors of dietary $K^+$ supplementation.

# DYAZIDE®

**25 mg** Hydrochlorothiazide/**50 mg** Triamterene/SKF

## Effective antihypertensive* therapy...without the bananas

* Not for initial therapy. See brief summary.

**Before prescribing, see complete prescribing information in SK&F CO. literature or PDR. The following is a brief summary.**

* **WARNING**

This drug is not indicated for initial therapy of edema or hypertension. Edema or hypertension requires therapy titrated to the individual. If this combination represents the dosage so determined, its use may be more convenient in patient management. Treatment of hypertension and edema is not static, but must be reevaluated as conditions in each patient warrant.

**Contraindications:** Concomitant use with other potassium-sparing agents such as spironolactone or amiloride. Further use in anuria, progressive renal or hepatic dysfunction, hyperkalemia. Pre-existing elevated serum potassium. Hypersensitivity to either component or other sulfonamide-derived drugs.

**Warnings: Do not use potassium supplements, dietary or otherwise, unless hypokalemia develops or dietary intake of potassium is markedly impaired.** If supplementary potassium is needed, potassium tablets should not be used. Hyperkalemia can occur, and has been associated with cardiac irregularities. It is more likely in the severely ill, with urine volume less than one liter/day, the elderly and diabetics with suspected or confirmed renal insufficiency. Periodically, serum $K^+$ levels should be determined. If hyperkalemia develops, substitute a thiazide alone, restrict $K^+$ intake. **Associated widened QRS complex or arrhythmia requires prompt additional therapy.** Thiazides cross the placental barrier and appear in cord blood. Use in pregnancy requires weighing anticipated benefits against possible hazards, including fetal or neonatal jaundice, thrombocytopenia, other adverse reactions seen in adults. Thiazides appear and triamterene may appear in breast milk. If their use is essential, the patient should stop nursing. Adequate information on use in children is not available. Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma. Possible exacerbation or activation of systemic lupus erythematosus has been reported with thiazide diuretics.

**Precautions:** The bioavailability of the hydrochlorothiazide component of 'Dyazide' is about 50% of the bioavailability of the single entity. Theoretically, a patient transferred from the single entities of triamterene and hydrochlorothiazide may show an increase in blood pressure or fluid retention. Similarly, it is also possible that the lesser hydrochlorothiazide bioavailability could lead to increased serum potassium levels. However, extensive clinical experience with 'Dyazide' suggests that these conditions have not been commonly observed in clinical practice. Angiotensin-converting enzyme (ACE) inhibitors can elevate serum potassium; use with caution with 'Dyazide'. Do periodic serum electrolyte determinations (particularly important in patients vomiting excessively or receiving parenteral fluids, and during concurrent use with amphotericin B or corticosteroids or corticotropin [ACTH]). Periodic BUN and serum creatinine determinations should be made, especially in the elderly, diabetics or those with suspected or confirmed renal insufficiency. Cumulative effects of the drug may develop in patients with impaired renal function. Thiazides should be used with caution in patients with impaired hepatic function. They can precipitate coma in patients with severe liver disease. Observe regularly for possible blood dyscrasias, liver damage, other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving triamterene, and leukopenia, thrombocytopenia, agranulocytosis, and aplastic and hemolytic anemia have been reported with thiazides. Thiazides may cause manifestation of latent diabetes mellitus. The effects of oral anticoagulants may be decreased when used concurrently with hydrochlorothiazide; dosage adjustments may be necessary. Clinically insignificant reductions in arterial responsiveness to norepinephrine have been reported. Thiazides have also been shown to increase the paralyzing effect of nondepolarizing muscle relaxants such as tubocurarine. Triamterene is a weak folic acid antagonist. Do periodic blood studies in cirrhotics with splenomegaly. Antihypertensive effects may be enhanced in post-sympathectomy patients. Use cautiously in surgical patients. Triamterene has been found in renal stones in association with the other usual calculus components. Therefore, 'Dyazide' should be used with caution in patients with histories of stone formation. A few occurrences of acute renal failure have been reported in patients on 'Dyazide' when treated with indomethacin. Therefore, caution is advised in administering nonsteroidal anti-inflammatory agents with 'Dyazide'. The following may occur: transient elevated BUN or creatinine or both, hyperglycemia and glycosuria (diabetic insulin requirements may be altered), hyperuricemia and gout, digitalis intoxication (in hypokalemia), decreasing alkali reserve with possible metabolic acidosis. 'Dyazide' interferes with fluorescent measurement of quinidine. Hypokalemia is uncommon with 'Dyazide', but should it develop, corrective measures should be taken such as potassium supplementation or increased dietary intake of potassium-rich foods. Corrective measures should be instituted cautiously and serum potassium levels determined. Discontinue corrective measures and 'Dyazide' should laboratory values reveal elevated serum potassium. Chloride deficit may occur as well as dilutional hyponatremia. Concurrent use with chlorpropamide may increase the risk of severe hyponatremia. Serum PBI levels may decrease without signs of thyroid disturbance. Calcium excretion is decreased by thiazides. 'Dyazide' should be withdrawn before conducting tests for parathyroid function. Thiazides may add to or potentiate the action of other antihypertensive drugs. Diuretics reduce renal clearance of lithium and increase the risk of lithium toxicity.

**Adverse Reactions:** Muscle cramps, weakness, dizziness, headache, dry mouth; anaphylaxis, rash, urticaria, photosensitivity, purpura, other dermatological conditions; nausea and vomiting, diarrhea, constipation, other gastrointestinal disturbances; postural hypotension (may be aggravated by alcohol, barbiturates, or narcotics). Necrotizing vasculitis, paresthesias, icterus, pancreatitis, xanthopsia and respiratory distress including pneumonitis and pulmonary edema, transient blurred vision, sialadenitis, and vertigo have occurred with thiazides alone. Triamterene has been found in renal stones in association with other usual calculus components. Rare incidents of acute interstitial nephritis have been reported. Impotence has been reported in a few patients on 'Dyazide', although a causal relationship has not been established.

**Supplied: 'Dyazide' is supplied as a red and white capsule, in bottles of 100 capsules; Single Unit Packages (unit-dose) of 100 (intended for institutional use only); in Patient-Pak™ unit-of-use bottles of 100.**

BRS-DZ-L42

a product of
**SK&F CO.**
Carolina, P.R. 00630

© SK&F Co., 1986

JOURNAL OF THE ARIZONA MEDICAL ASSOCIATION

ARIZONA MEDICINE

MAY 1987, VOL. XLIV, NO. 5

# The "Real" World

Marshall B. Block, M.D.

While looking for a "good used car" for my daughter, we stopped at an automobile dealership known for its integrity. After duly kicking tires, we found a vehicle we both liked. As the salesman was doing whatever they do with their "managers," I found the original owner's name in the glove compartment and phoned her while we waited. Although we were assured the car was never in an accident, had never been repainted ("original paint"), and was in perfect mechanical shape, the former owner told us just the opposite, i.e., the car had two accidents, front and back, was painted at least twice, and had a major oil leak, the origin of which was never found. When confronted with this information the salesman feigned total surprise and disbelief, and vowed to remove the car from the lot and "wholesale it." The next day I decided to call the dealership and ask about the vehicle. By chance, the same salesman answered the phone but he obviously didn't recognize my voice. "I saw a car on your lot last night that I liked and I was wondering what kind of condition it was in," I asked. He answered, "It's never been in an accident, mechanically it's perfect, and it has its original paint." Such a lesson for a 17-year-old girl to learn! Had it come from my lips or from her schoolteachers or her religious advisers, I don't think she would have believed us. She learned about the real world from a used car salesman!

We, on the other hand, as physicians, live in a dream world. Our daily lives revolve around our chosen profession. For most of us, we enjoy and get a great deal of satisfaction doing what we do "for a living." We get up and feel clean, shower and look clean, we enter a clean work environment whether in our office or in the hospital. We don a white coat (or pastel color) or clean surgical garb. We interact and interview our patients in an upfront, honest fashion. For the most part our conversations with our patients are honest, truthful and above-board. Our patients come to us for help and we reciprocate the best we can. We don't have to deceive, lie or con them. We just have to be compassionate and honest. They in turn deal with us, for the most part, honestly. They don't withhold information if they are seeking our help. For some it might take a bit of time to get it all out, but it does eventually come out. We furthermore serve on committees at hospitals and in professional and civic organizations. We arrive on time, we give it our best when asked to perform or give an opinion whether it's private or in a public forum. We have been raised as responsible persons to do what is right and what is intellectually honest. The scientific method plus the wisdom of the Judaic-Christian religions have been melded to give us a code of ethics which we all follow whether we realize it or not. When we don't, we feel guilty. Sometimes the guilt is overwhelming, for our aspirations are higher than our attained goals. For some of us this leads to behavior which is socially unacceptable and self-destructive, i.e., alcohol abuse, drug abuse, and even suicide. Thankfully, most of us can survive the demands of our profession and prosper. But, when the pressures build or when our sleep is interrupted by a call from the hospital or a disgruntled patient phones, remember what it must be like to be a used car salesman in the "real world" and be thankful for our role in the scheme of things. We are in a unique profession. ■

**Marshall B. Block, M.D., Editor**

JOURNAL OF THE ARIZONA MEDICAL ASSOCIATION

ARIZONA MEDICINE

MAY 1987, VOL. XLIV, NO. 5

*Arizona Medicine* is a socioeconomic and scientific journal published monthly by The Arizona Medical Association, Inc., 810 West Bethany Home Road, Phoenix, Arizona 85013, in conjunction with *The Western Journal of Medicine*. All views and opinions expressed in the articles published herein are the authors' and may or may not reflect those endorsed by The Arizona Medical Association.

(602) 246-8901 in Phoenix
1-800-482-3480 Statewide

Neil O. Ward, M.D.
*President*
Bruce E. Robinson
*Executive Vice President*
Misty Coumbe
*Assistant Executive Vice President*
Chic Older
*Assistant Executive Vice President*

Marshall B. Block, M.D.
*Editor*
Thomas J. Marks
*Manager of Publishing*
Susan Fuchs
*Communications Director*
Linda N. Brown
*Editorial Assistant*

Please notify publisher at least six weeks prior to change of address and include old and new addresses and a mailing label from most recent copy of *Arizona Medicine*. Include your new postal Zip Code number.

**IN THIS ISSUE . . .**

- The Normal Man
  *William B. McGrath, M.D.*
- Teaching Ethical Issues to Medical Students
  *University of Arizona*
- Medicare Assigned and Unassigned Claims
  *Richard E. Kirkpatrick*
- Lifesaving Blood Loop
  *Susan Fuchs*
- New Active Members
- Children's Miracle Telethon
  *Amy Petrovsky*
- ArMA Annual Meeting Schedule
  *Pgs. 9 & 18*
- Physicians in the News
- Medical Facts

## From Our President

Neil O. Ward, M.D.

# Who is Drug Free?

The U.S. Military reduced drug use by 67% between 1981 and 1986. It cost the U.S. Navy $2 million each month for drug testing of Navy personnel, but it proved cost-effective. Teachers from Dade County (Florida) and the police force in Miami are participating in successful drug testing programs.

I suspect most physicians believe our obligation to public safety (by performing our task drug-free) is at least equal to that of airline captains, firemen, policemen, teachers, and amateur athletes. As role models who would submit to voluntary body fluid testing, we could emphasize that drug use causes individuals twice as much illness, three times the accidents, and one-third less productivity than drug-free citizens enjoy.

A mandatory drug-testing program is not only unconstitutional, but unworkable. The issue here is not civil liberty. It is health and safety — the health of our colleagues and the safety of our patients. This is not a suggestion that anyone be considered guilty of drug use 'til proven innocent; it is a plea to recognize that many of our colleagues have health problems involving drug or alcohol abuse. They deserve to be identified as much as our patients do. And, when diagnosed, deserve our best treatments. Therapy is available through ArMA's Physician's Health Committee.

In anticipating a voluntary body fluid testing program, the concern about "false positive" results can be assuaged by increasingly sensitive testing methods and the requirement that all positive results be retested. Professor Banzhaf, writing in the January 12, 1987 *National Law Journal*, explains the constitutional acceptability of "facilitative searches," such as fire marshalls and building inspectors conduct, designed to correct problems, not punish.

There are other physician health concerns — such as hypertension, malignancies, and senility. Physicians organized as hospital medical staffs have the interest and intelligence to offer a health evaluation to colleagues — to include voluntary body fluid testing — at time of appointment or reappointment to the medical staff and for cause. The program design for reliability, confidentiality and decisions to react should remain firmly in the grasp of the physicians.

As physicians, we have an obligation to our communities to preserve the health of our colleagues and to protect the safety of our patients. Who will be the first Arizona hospital medical staff to demonstrate this duty can be done? ■ **Neil O. Ward, M.D., President**

# MICA

## IN ITS SECOND DECADE
## OF PROVIDING QUALITY
## MEDICAL MALPRACTICE INSURANCE

## LIMITED TO ARIZONA PHYSICIANS
## WHO ARE PREFERRED RISKS

For more facts, please call the MICA Underwriting
Department (602) 956-5276
or toll free (800) 352-0402

MICA MICA MICA MICA MICA

MUTUAL INSURANCE COMPANY OF ARIZONA Sponsored by: Arizona Medical Association
Arizona Osteopathic Medical Association

# The Normal Man

William B. McGrath, M.D.

May we introduce a normal man? Or a personification of the normal man?

Since considerable self-doubt goes with being normal, such an individual can never be convinced how normal he is. Here we have a dilemma. Because of his religious background the normal chap would feel a little queasy if he used the more precise word, conundrum. He winces when they call it a "rubber" of bridge. Better to chew one's food than to masticate.

In the hermetic privacy of his car, disgusted with himself for failure to keep a resolution, the normal man will say the vulgar words for feces or fornication. And when he growls his blasphemous opinion of the whole world, he counterbalances or hedges with a sheepish apology to God.

Our friend cannot tolerate any blemish of his complexion. He will pick at it until he will have tunneled halfway to China. There is something remotely erotic in the successful extrusion of a blackhead. It is (Watch it!) a microorgasm. He can tell at a glans that the manicurist, pushing back the cuticle, is a miniature rabbi.

We're getting a bit too cutesy, eh?

The drooping of his lower lids (ectropion) is due to his repeatedly pulling them down in order to instill vasoconstricting eyedrops. Still they do not screen the bloodshot evidence of his mild dependency on alcohol. Does he have a drinking problem? His only problem is how to get rid of the empties. He rotates his purchases, ashamed to have any one liquor store proprietor recognize how much he buys. (Whoever wrote the book on alcoholism, "Just One More," certainly chose an apt and unforgettable title.)

Our normal man is a closet hypochondriac. The tiniest nip of pain must surely be cancer, until proven otherwise. In social situations or in restaurants he is never quite relaxed. So his stomach balloons. He loosens his belt and furtively unbuttons the top of his fly. He doubts that women ever break wind as men do. He had rather not defecate in the dark because it is so important to see the color and consistency of his stools.

He is quite shy, moreso than might appear, and his shyness as always is at his friends' expense. He waits for someone to call, wistfully at first and then patiently and then with shades of resentment and self-pity and self-blame. Everyone else is popular and busy with hobbies and having fun. In his case any social or recreational engagement has to be initiated by others, or by his wife. She does not anticipate rejection, as he does, and he secretly admires her uncomplicated friendliness or obtrusiveness in using the telephone.

On rare occasions he has paid a seemingly spontaneous visit. But his nervousness is betrayed by inappropriate profanities and by his talking too much and too loudly about himself. It is as if he is thinking: If you knew more about me you might be less disposed to dislike me. His yearning for familiarity is trapped behind the barbed wire of derisive humor.

The life of our normal man has been relatively innocent. For this he does not give himself credit, or deserve it. He has always been ready and willing to transgress; to be seduced, for example, or to get revenge on anyone who has slighted him—but anonymously, of course. He has been deterred only by lack of opportunities and by fear of getting caught and losing face. The bosomy blonde nymphomaniac in the convertible, as in the dirty movies, never did notice him standing on the corner. He is not looking for an actual affair, just wanting reassurance that he could have one if he chose to. And, oh, does he flirt! Defensively he rationalizes: "Well, I am just as cordial and attention-

seeking with men as with women."

His puritan conscience forbids him to enjoy life. Parole is granted only by way of comradeship or treacherously with alcohol.

His naked body is as ugly and obscene as a basset hound. He still cannot conceive or be convinced that a woman might desire physical contact with a spigotty male.

Our (exemplified) normal man feels inferior to most of his colleagues. They all seem so sure of themselves, so poised, so—equestrian term—collected. They have talents and interests and investments which he lacks.

Oh, of course there are a few know-it-alls. They can talk glibly on any topic, with bubbles of information and froth of cliches. Their pronouncements are prefaced by such phrases as, "in terms of" or "basically" or "so to speak" or "shall we say." (During an unwelcome consultation a neurotic minister kept interrupting himself, "Now let me insert this.")

Aside from his work our friend has made no commitments, acquired no expertise. He has frittered away his intelligence. He is a joatmon. (Whoopee! That's acronym for jack of all trades, master of none.)

His resolution to keep a journal or diary lasted about as long as his switching from cigarettes to a pipe. He did intend to write. But anything he knows has already been written, and by smug professionals. He has the mind of a frog, jumping every which way or squatting on some old tune, repeating it over and over again, with a few remembered parts of the lyric.

He looks askance, sidewise, at criteria for the diagnoses of personality disorders. He fits every description. At times he has been manic-depressive or schizoid or paranoid. At other times he has been hysterical or passive-aggressive or obsessive-compulsive or sociopathic. His self-esteem is like melting snow.

The normal man has come to realize that the most poignant longing of all is not for love or sex or security or power or fame. One's longing is for an opportunity to tell the whole story of his or her life, the whole unedited, unexpurgated edition of the book. Cardinal Newman entitled his, Apologia Pro Vita Sua, the first word meaning explanation, not apology. One presumes that God, and only God, will hold judgement until the book is closed. ■

**William B. McGrath, M.D.**


**MEDICAL BOOKSTORE**

**MEDICAL BOOKSTORE**
College of Medicine
Arizona Health Sciences Center
Tucson, Arizona 85724
Phone: 626-6669

**TAX & PENSION**
**DESIGNED**
**REAL ESTATE FINANCING**

Residential Refinancing
New Purchases
Small Medical Office Buildings

***LOW RATES — MINIMAL POINTS***

No Charge To You For
Tax Designed
And
Pension Oriented
Mortgages

**MARVIN H. BENDAU**
**MORTGAGE BROKER**
**943-7229**

# The Teaching of Ethical Issues to Medical Students

From the beginning of the College of Medicine, ethical issues in medicine have been a matter of interest and concern in the education of students. When the Human Behavior and Development course was introduced into the required basic science curriculum in 1973, instruction about ethical issues became a part of the formal curriculum. The year-long course meets twice a week and the two-hour sessions always include time for student discussion. The Human Behavior and Development course has a primary focus on the psychological and sociological aspects of medical problems and the doctor-patient relationship. It does, however, provide an arena for all students to become acquainted with the topic of medical ethics. Students are encouraged to think about and sort out for themselves the kind of approach to particular ethical issues that will be appropriate for them and for their patients.

Ethical issues are included in almost every class session. For example, class sessions dealing with childbirth, child development and child abuse, eating disorders, chronic illness and health care delivery systems, among others, have important ethical considerations embedded in them. Often the ethical questions in the sessions are not the "big issues" discussed in today's newspaper, but involve intertwined ethical and medical issues. For these sessions, we try to help students identify and separate the ethical and the medical issues and then examine the various ways of approaching the ethical components.

Other sessions are focused much more specifically around particular ethical issues. The faculty for these sessions may include philosophers, clergy, psychologists, nurses, social workers, and physicians. The topic is introduced either by lecture, videotape, a panel discussion, or some combination of these. After the presentors describe the problem and their perspective on that problem, the discussion is expanded to include the concerns and questions of the students. Typically there is no "one right answer" and students are encouraged to explore all the options related to the particular issue, both during the class session and in thinking about the issue at a later time. One example of topics that are discussed in this more detailed way is genetic counseling and the related ethical questions. For example, the students are challenged to consider the pros and cons of amniocentesis for sex determination only. This procedure brings into sharp focus vitally important ethical issues, namely population control and proportional representation of the sexes.

Abortion is another issue which is looked at in depth. Two class sessions are scheduled, with one session presenting the views and perspectives of medical personnel who support abortion as an option and another session which presents the views and perspectives of medical personnel who oppose abortion as an option. The two sessions give the students the opportunity to interact with the presentors and voice their concerns and opinions about the issue. Our approach is to encourage a thoughtful discussion of this difficult topic, keeping the lines of communication open between people with differing views. No student is asked to take a stand for or against the issue but rather to consider the range of views involved.

Legal issues are necessarily discussed along with the ethical issues and include such topics as the legal risk of being a medical student, questions related to who owns the medical chart, what is privileged communication and what does it mean, what is the place of surgical intervention for a retarded newborn, how is death diagnosed, and when do we use life support and when not.

In summary, there is coverage in the course of the "every-day" ethical questions, attention to medical-legal issues, and attention to some of the medical ethical issues that generate serious and concerned discussion in the general population and in the medical profession. We are providing experiences in a non-threatening classroom setting that we believe will later be useful in the student's professional career.

Additional opportunities to explore ethical issues occur in connection with topics covered in other basic science courses, although necessarily there is less focus on the ethical issue. The students in their last two years of medical school will be exposed to many patients with ethical problems. The setting will be clinical, the problems immediate and real.

We believe the experiences they have had in the Human Behavior and Development course will allow them to grasp more effectively the significance and complexity of ethical issues they encounter in their clinical training. ■

**Shirley Nickols Fahey, Ph.D.**
**Coordinator, Human Behavior and Development**

**Herbert E. Pollock, M.D.**
**Coordinator, Human Behavior and Development**

**Louis J. Kettel, M.D.**
**Dean, College of Medicine**
**University of Arizona**

## Medicare Assigned and Unassigned Claims: What Do They Mean?

In our consulting work, as well as in our workshops, we continue to find large numbers of physicians, office managers, billing, and insurance personnel who do not understand the fundamental differences between assigned and unassigned Medicare claims, and the practice's and patient's rights and obligations. The errors that continue to occur relative to these terms have cost, and will continue to cost, thousands of dollars for individual practitioners throughout the United States. Not only does this do the practice a disservice, but it also does a disservice for patients in general because it may result in doctors raising fees to their non-Medicare patients to much higher amounts than might otherwise be necessary.

Arizona's Aetna/Medicare organization publishes a booklet entitled, *Aetna's Guide to Medicare - Part B* which is currently in its sixth edition, and is somewhat out-of-date. Unfortunately, the booklet was published prior to the passage of public law 99-509, the OBRA law, passed in October 1986, dealing with Maximum Allowable Actual Charges (MAAC). It is not our intent to explore the implications of that law, because they are far too complex to discuss in a journal article. We feel it is essential, however, to explain the rules and regulations pertaining to assignment and non-assignment of Medicare benefits. We would still strongly suggest that every practitioner in the State write to the Professional Relations Department of Aetna-/Medicare, and request a copy of this booklet (the address is at the end of this article.).

*Assignment of Medicare benefits* means that both the doctor and the patient have agreed and authorized Medicare to forward payment directly to the physician. By the physician's agreement to do this, the physician also agrees that he will accept whatever Medicare *approves* as payment in full. Note that the operative word here is "Medicare *approved*." Medicare will forward a check to the doctor for 80% of the *approved* amount. *This does not necessarily represent the maximum amount that the physician may collect from the Medicare patient*. Except in the case of certain pathology procedures, and certain outpatient surgery procedures approved by Medicare, the patient will be liable for both an anual deductible of $75, as well as a *co-payment of 20% of the Medicare approved amount*. For instance, if the doctor's customary fee or MAAC was $140, but Medicare *approved* $100 (because the doctor has agreed to accept Medicare's *allowed* amount through assignment), Medicare would forward a check to the practitioner in the amount of $80. This would leave the patient, or the patient's co-insurance company, with a balance of $20 (20%) of the Medicare *approved* amount. When a doctor agrees to accept assignment, he agrees that no additional amounts over and above the Medicare *approved* amount will be billed to the patient, or to the patient's supplemental insurance carrrier.

Unfortunately, many physicians and medical office insurance personnel believe that the payment (80% of the *approved* charge) is all they are entitled to, and all they may collect when they have accepted assignment from Medicare. Not only is this an incorrect interpretation of assignment, it

may be considered a technical violation of the Medicare regulations, potentially resulting in money penalties, but, much worse, it may result in the doctor's customary fee profile or MAAC being reduced during the next fee screen period. In the example cited above, if the doctor accepted the $80 as payment in full for the service on all of his Medicare patients, he might find his customary charge or MAAC reduced to $80 during the next calendar year. This would mean that in that following year, the doctor's approved charge would be $80 instead of $140. Consequently, the doctor would receive only $64 from Medicare on assigned claims. In the case of non-participating physicains, the doctor's new MAAC of $80 would be the maximum he would be allowed to bill for these services, *whether he accepted assignment or not!*

Most physicians accept assignment from Medicare patients on a case-by-case basis. This is the major reason we have found for physicians choosing not to participate in the Medicare program. A non-participating physician can elect to accept assignment on one Medicare patient and not accept it on another; he may accept assignment today on a Medicare patient for hospital services, and not accept assignment on the patient tomorrow for office services, or vice-versa. Participating physicians, on the other hand, must accept assignment on all Medicare patients at all times. A Medicare patient surviving on a minimum Social Security income would probably not have enough money to pay for supplemental insurance. In these situations, if the doctor elects to accept Medicare payment as payment in full, he may do so, although we suggest that the doctor place the patient through their normal billing cycle before reaching such a decision. If the money is truly uncollectible, Medicare cannot hold the physician responsible for not collecting it. However, no one would be able to accept the fact that *all* of the Medicare patients in a medical practice could not pay the co-insurance.

One added pointer for particpatig physicians is that *it is authorized* for them to collect deductibles and co-payments when the patient is in the office. This was explicitly described in the fact sheet distributed to physicians in November of 1986 on the implementation of public law 99-509 (the famous "Dear Doctor" letter.).

*Non-assigned Medicare claims* are only possible when a physician has elected to be a non-participant in the Medicare program. If a physician is a non-participant, he may elect to bill a patient his full Maximum Allowable Actual Charge (MAAC), even if this charge is in excess of the prevailing Medicare charge for the area. In those situations in which the doctor's MAAC is in excess of the Medicare prevailing amount, and he chooses not to accept assignment, the doctor is entitled to collect the fee up to the full MAAC amount. For example, if the doctor has a MAAC of $155 for a procedure and Medicare has a prevailing fee for that procedure of $110, *the doctor may hold the patient responsible for the entire charge.* In this situation, *the patient would receive the Medicare check* for $88. If the patient has co-insurance through AARP or some

**PRACTICE MANAGEMENT PROBLEMS?**

**DO ANY OF THESE SOUND FAMILIAR?**

- Declining Patient Volume and Practice Income
- Increasing Overhead
- More Competition Than Ever Before
- Demanding Patients
- Confusion Over Governmental Reimbursement Plans
- Skyrocketing Malpractice Insurance Premiums
- Confusing Contracts from Prepaid Health Plans

While it may not be possible to eliminate all of these problems, it is possible for medical practices to control at least a portion of these challenges through effective Practice Management.

The Professional Practice Division of Toback & Company can provide marketing advice which will increase patient volume; financial tools to increase income and control overhead; reduce office conflict and personnel management problems, reducing employee turnover; and increase physician satisfaction with the practice. Richard E. Kirkpatrick, M.H.S.A., Manager of our Professional Practice Division and a nationally recognized authority on medical practice management can provide you with additional information on the benefits of our services in a no-fee interview. Please call 264-9011 to schedule an appointment.

**TOBACK & COMPANY, P.C.**
Professional Practice Division
3200 North Central Avenue, Suite 700
Phoenix, Arizona 85012
(602) 264-9011

Richard E. Kirkpatrick

other similar retirement program, the retiree program would, in most cases, pay the difference between the $88 and the $110 Medicare prevailing fee, $22. The patient would then owe $45 out of his own pocket. It should be noted that some Medicare supplementary carriers will pay the entire difference between the doctor's Maximum Allowable Actual Charge and the Medicare approved amount. In fact, most so-called "high option" Medicare supplemental plans have such provisions. Unfortunately, it's very difficult to ascertain which patients have these "high option" plans, other than by reviewing the policy.

Whether a practice is participating or non-participating, they can have a Medicare patient sign a lifetime authorization for assignment of benefits. The statement that the patient must sign is listed on page 7 of the booklet, *Aetna's Guide to Medicare - Part B.* Once this lifetime assignment is accepted by the physician, he may then submit claims to Medicare by simply inserting the phrase "patient's request for payment on file" in blocks 12 and 13 of the Universal Claim Form (HCFA-1500). It should be noted that in order for assignment to be accepted by Medicare, block 13 must have the patient's signature or the statement listed above inserted, *and* the doctor must indicate his acceptance of assignment in block 26 of the Universal Claim Form. If this block is not checked, Medicare will assume that assignment is not accepted, and payment will be forwarded to the patient.

In conclusion, doctors must understand that accepting assignment does not mean that the payment received from Medicare is payment in full for Medicare-assigned services. Furthermore, doctors must understand that it is always essential that they charge their full Medicare approved charge for all services rendered to Medicare patients. If this is not done, it may have a detrimental effect on the doctor's customary (for participating physicians) fees or on the doctor's Maximum Allowable Actual Charge (for non-participating physicians) in coming years. Practices are strongly encouraged to contact the Provider Relations Department of Aetna-Medicare, P.O. Box 37200, Phoenix, Arizona 85069 for the booklet mentioned above, if they have not already received a copy. ■

**The Professional Practice Division**
**Toback & Company, P.C.**
**Richard E. Kirkpatrick, H.H.S.A.**
**Manager**

# The 96th Annual Meeting

of the

# Arizona Medical Association

will be held

## June 4 - 6, 1987

at

## The Pointe at South Mountain

7777 South Pointe Parkway, Phoenix, Arizona

**THURSDAY, JUNE 4**
All Day
Current Perspectives
C.M.E. Programs

Evening
Casual Reception
Dinner

**FRIDAY, JUNE 5**
6 a.m., Executive Committee
8 a.m., Board of Directors
10 a.m., House of Delegates

Noon, Past Presidents' Luncheon
2 p.m., Reference Committees
President's Reception & Banquet

**SATURDAY, JUNE 6**
8 a.m., House of Delegates
Noon, Board of Directors

AIM HIGH

# A PRESCRIPTION FOR PHYSICIANS

**BOTHERED BY:**

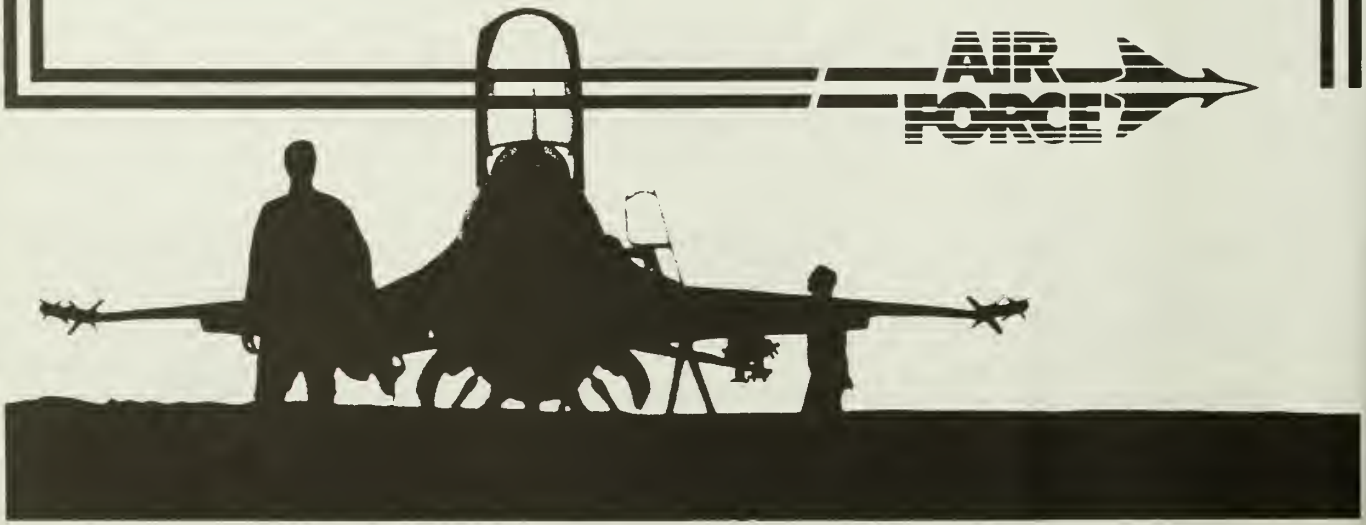
- ★ Too much paperwork?
- ★ The burden of office overhead?
- ★ Malpractice insurance costs?
- ★ Not enough time for the family?
- ★ No time to keep current with technology and new methods?
- ★ No time or money for professional development?

**JOIN THE AIR FORCE MEDICAL TEAM; WE'LL PROVIDE THE FOLLOWING:**

- ★ Competent and dedicated professional staff.
- ★ Time for patients and for keeping professionally current.
- ★ Financial security, a generous retirement for those who qualify.
- ★ If qualified, unlimited professional development.
- ★ Medical facilities all around the world.
- ★ 30 days of vacation with pay each year.
- ★ Complete medical and dental care.
- ★ Low cost life insurance.

Want to find out more? Contact your nearest Air Force recruiter for information at no obligation. Call

**(602) 921-9582**
**collect**



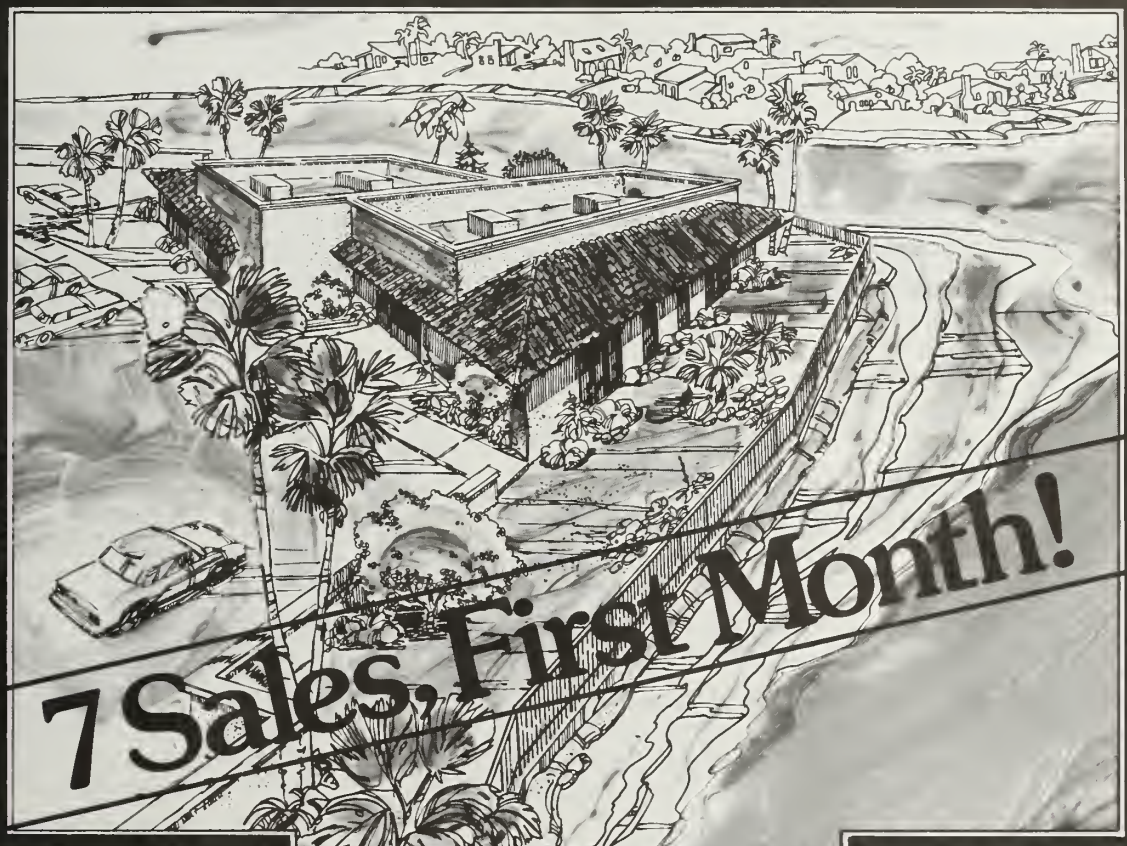
AIR FORCE

AN OUTSTANDING LOCATION □ A REMARKABLE VALUE

# *Bank Sale Presents A Unique Opportunity.*

Practice at a premium location on the shore of Dobson Ranch Lake, part of the Dobson Ranch planned community. Located just south of the Dobson Road and Baseline intersection, a short drive from Desert Samaritan and five other East Valley Hospitals.

Enjoy the tax benefits of an owner-occupied medical office that features easy freeway access, open space, individually signed identity, ample parking at your door and street level entry with in-and-out ease for handicapped patients. Choose from eighteen separate units in seven building clusters.




## Dobson Ranch Professional Center

2058 South Dobson Road □ Mesa, Arizona

Managed and Marketed by
**Lowe Associates, Inc.**

**Contact your local Broker or Telephone Peter Koenig, 279-0120**

# New Active Members . . .

*The Arizona Medical Association welcomes the following new members:*

COCHISE

**John W. Clarke, M.D.**
Family Practice
302 El Camino Real
Suite 3, Sierra Vista
University of Louisville
School of Medicine - 1951

MARICOPA

**Nicholas J. Argyros, M.D.**
Pediatrics
6135 North 7th Street
Phoenix
University of Arizona
College of Medicine - 1982

**David P. Goldstein, M.D.**
Anesthesiology
7008 East Osborn Road
Phoenix
Yale University
School of Medicine - 1982

**Deborah Nemiro, M.D.**
Obstetrics & Gynecology
4616 East Shea Boulevard
Suite D230, Phoenix
George Washington University
School of Medicine - 1979

**Marc A. Petein, M.D.**
Cardiovascular Diseases,
Internal Medicine
13260 North 24th Drive
Suite 110, Peoria
Fac De Med De L'Univ
Cath De Louvain - 1975

**Ray F. Rhodes, M.D.**
Anesthesiology
5060 North 19th Avenue
Suite 103, Phoenix
University of Oklahoma
College of Medicine - 1970

**Raffy A. Safarian, M.D.**
Internal Medicine
6641 East Baywood, Mesa
Fac De Med Univ
De L'Etat Liege - 1982

**Armando M. Sulit, M.D.**
Anesthesiology
635 West Indian School Road
Suite 108, Phoenix
Manila Central University - 1967

**Elton S. Thayer, M.D.**
Anesthesiology
2000 North 7th Street
Phoenix
University of Oregon
School of Medicine - 1981

**Stanley D. Walker, M.D.**
Ophthalmology
9221 North Central Avenue
Phoenix
Mayo Medical School - 1981

YAVAPAI

**Fred S. Markham, M.D.**
Internal Medicine
434 West Gurley Street
Prescott
University of Arizona
College of Medicine - 1980

**Kevin J. Prendiville, M.D.**
Ophthalmology
300 South Willard Street
Suite 107, Cottonwood
Medical College of
Wisconsin-Milwaukee - 1980

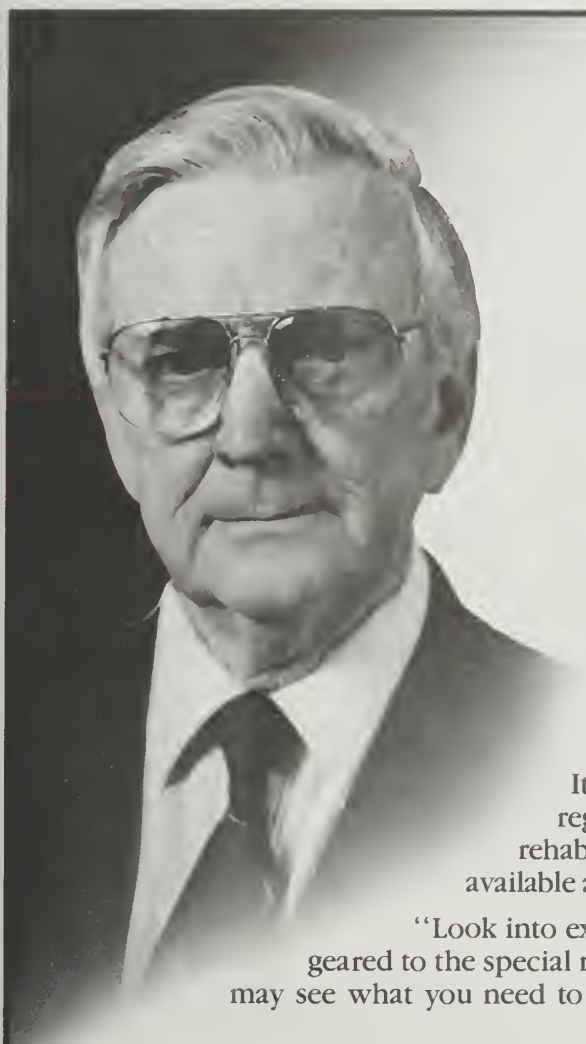
YUMA

**Thomas Podolsky, M.D.**
Ophthalmology
2451 South Avenue A
Suite 6, Yuma
University of Arizona
College of Medicine - 1981

NEW RESIDENT MEMBER

PIMA

**Thomas L. Brysacz, M.D.**
Family Practice
1450 North Cherry, Tucson
University of Arizona
College of Medicine - 1984



Extended Care: No. 1 in a Series

**"Your most loyal customers are also the fastest growing segment of the health care population. And they depend on you for their alternate care decisions."**

– James L. Grobe, M.D.
Medical Director
Helen C. Lincoln
Extended Care Center

"For this reason, I'm impressed with the concept of extended care. Extended care is skilled, quality care. It's administered in close cooperation with the patient's regular physician. Moreover, it's designed to restore and rehabilitate, which yields happier, healthier patients. And it's available at a cost that satisfies the new cost-conscious pay systems.

"Look into extended care today. You'll see a host of sound practices, geared to the special needs of your fastest growing patient base. And you just may see what you need to insure your own healthy future."

## Get the Facts about Extended Care!

Call or write for your free copies of the Bryans Center or Helen C. Lincoln Care Center portfolios and the latest Medicare guidelines for nursing homes. Ask one of our administrators or social service directors for assistance with your patients – they can help with everything from extended and long-term care to a full range of rehabilitation services, even home health or adult day care. Call us or stop by for a personal tour...you'll like what you see!

**Adjacent to John C. Lincoln Hospital**
Located just steps away from John C. Lincoln Hospital & Health Center, Bryans Center has full access to the resources and specialty services of the hospital.

**Administrator: Lynn Davies**

944-1666

BRYANS CENTER
9155 North 3rd Street
Phoenix, AZ 85020-2460

**Adjacent to Thunderbird Samaritan Hospital**
Located on the Glendale campus of Thunderbird Samaritan Hospital & Health Center, adjacent to retirement communities, medical offices and shopping.

**Administrator: Sid Roberts**

843-8433

HELEN C. LINCOLN EXTENDED CARE CENTER
13620 North 55th Avenue
Glendale, AZ 85304-1399

Affiliates of Lincoln Health Resources

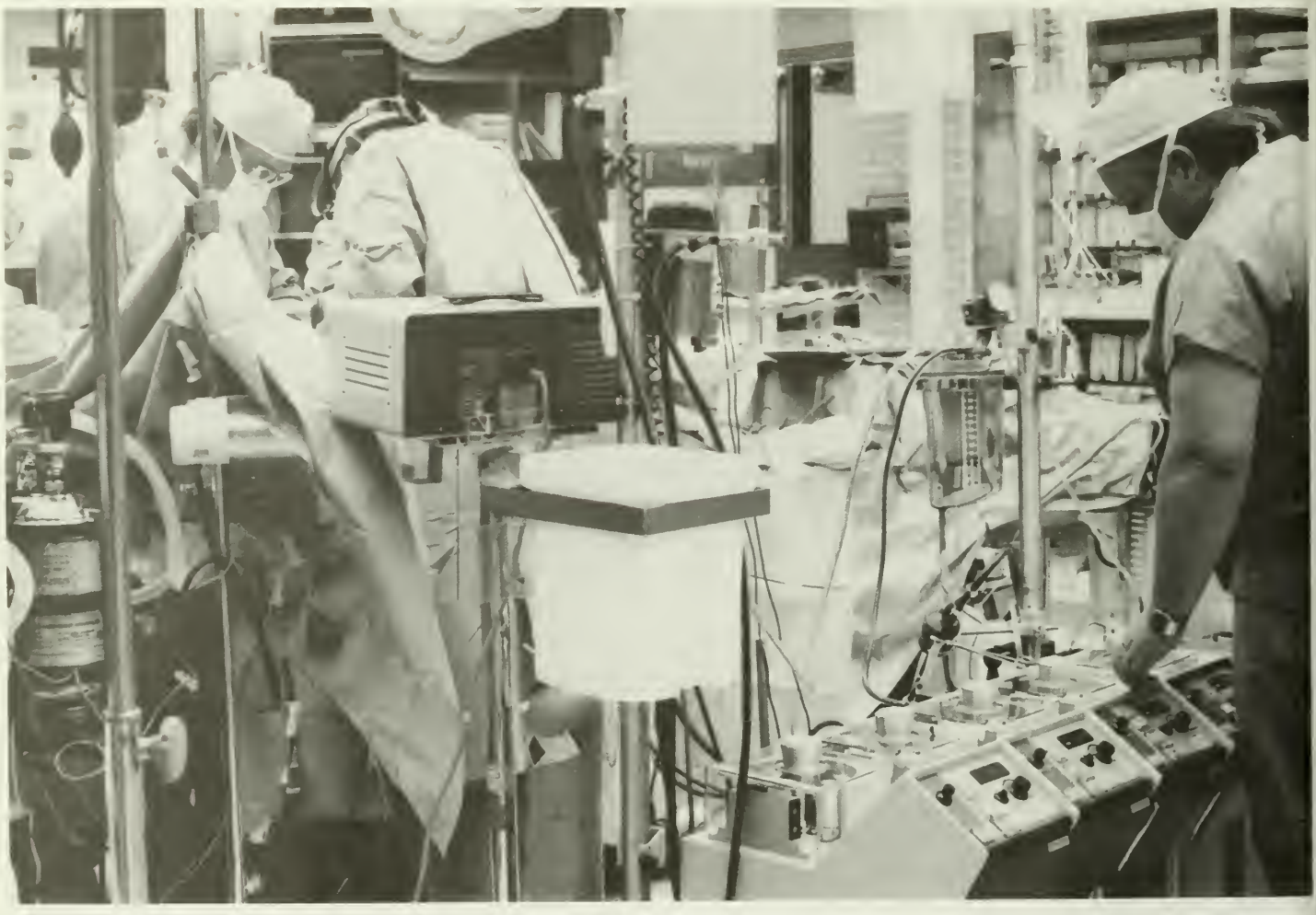


Photo by Susan Fuchs

**New Sarns Safety Loop, invented by Phoenix perfusionist Jon Austin, right, and cardiovascular surgeon Cecil C. Vaughn, M.D., center, is part of the conventional heart-lung bypass blood pump, foreground. Austin monitors the machine as Dr. Vaughn and James G. Lawson, M.D., left, perform cardiac bypass surgery at Phoenix Baptist Hospital. Pat Lowell, R.N., far left, assists.**

# Phoenix Surgeon, Perfusionist Invent Lifesaving Blood Loop

When the warning sound from a conventional heart-lung bypass machine alerts its perfusionist to the presence of a low operating blood level, the medical technician has precious few split seconds—if any—to act. The perfusionist must instantly shut the machine down to stop air bubbles from entering the patient's body where they can cause brain damage or death.

Occasionally, at the instant the warning sounds, it is already too late

What surgeons and their perfusionists have needed since the first bypass machine was used in 1953 was a device which would automatically shut the machine down the instant an errant bubble was detected, a device to transcend the human limitations of even the most alert and responsive perfusionist.

Such a device could save the lives of the estimated 200 patients who die each year as a result of unavoidable air embolisms. Such a device could prevent neurological damage to the lucky patients who survive air embolisms.

And such a device has been invented by Phoenix cardiovascular surgeon Cecil C. Vaughn, M.D., and perfusionist Jon W. Austin, C.C.P. After five years of testing and approval-seeking, a version of their device, which they call a perfusion loop, was approved for marketing in early March by the federal Food and Drug Administration (FDA).

**. . . could save 200 lives a year.**

Although the loop's initial approved function during heart surgery is to gently evacuate

**Continued**

## Organ Bank Opens First Bone and Tissue Center in Southwest

The Arizona Organ Bank at Good Samaritan Medical Center announces the opening of the Phoenix Tissue Bank, the Southwest's only complete bone and tissue procurement center. The new center is one of five facilities in the nation equipped to remove and process human bone and tissue under sterile conditions.

For the first time in the Southwest, the Phoenix Tissue Bank will provide complete processing capabilities to other procurement agencies. Prior to the opening of this facility, sterile tissue procurement in Arizona had to be conducted exclusively in hospital operating rooms and the tissue had to be shipped to the East Coast for processing. The Tissue Bank features a sterile procurement and processing rooms which allow for all tissue banking services to occur in the same facility.

"Having all the steps of this process under one roof means we can save time in providing bone and tissue for surgical procedures and at the same time control costs," said Tom Hagan, Technical Director of the Tissue Bank.

Bone and tissue is used for numerous surgical procedures including spinal fusions, replacement of bone loss due to trauma or cancer, repair of shoulder separations, ligament tears, total joint replacements and plastic surgery procedures.

The Phoenix Tissue Bank is located on the third floor of the Edwards Medical Plaza, 1300 North 12th Street, Suite 300, Phoenix.

## Lifesaving Loop
(Continued)

blood from the main chamber of the heart, gently enough to avoid damaging fragile blood cells, the loop's ultimate purpose is to stop the flow of air bubbles which can cause stroke, neurological damage and even death.

The need for the loop was first articulated by Dr. Vaughn after he testified in a court case involving a Tucson heart surgery patient who died after a stroke which was caused by an undetected air bubble in the brain.

"There really ought to be a way to prevent that," Dr. Vaughn told Austin, with whom he has worked for almost 20 years. A few mornings later, Austin strolled into Dr. Vaughn's office with the prototype perfusion loop. "Jon is an engineering genius," Dr. Vaughn said.

The perfusion loop is an interconnected tube within a tube. Inserted into a conventional roller-type blood pump housing, its outer tube is similar to conventional blood pump tubing. Its inner tube, however, is very thin and collapsible. It collapses instantly if inlet pressure is less than zero, which happens when air bubbles are present. The tubal collapse prevents the pump from circulating both blood and air, which gives the perfusionist time to prevent the air embolism from reaching the patient.

> "Jon's an engineering genius."

Manufactured by Sarns, a division of the 3M Company, the initial device is marketed as the Sarns Safety Loop.

"Sarns refined our original design during the manufacturing process," Austin said, "but the concept is the same. It works like a straw which collapses under negative pressure and prevents anything from traveling through it.

The loop was first used in Phoenix by Austin and Dr. Vaughn, and is now available for use in hospitals nationwide. ■

# Children's Miracle Telethon In Phoenix

Another chance to "help make miracles happen" for sick and injured children in Arizona is being offered to the community in the upcoming Children's Miracle Network Telethon. Phoenix Children's Hospital will once again participate in this special event on Saturday, May 30, and Sunday, May 31, as KTSP Channel 10 broadcasts the Telethon live in Phoenix.

Last year the Children's Miracle Network Telethon in Phoenix raised $313,000 to assist Phoenix Children's Hospital in providing care for children with special medical needs.

The Telethon is produced nationally by the Osmond Foundation. Established by the Osmond Family, the Foundation's goal is to raise funds to improve the health of children through research, medical services and education.

The Children's Miracle Network Telethon has been characterized by dramatic growth over its short, five-year period. Today it is the second largest Telethon in the world.

"In 1986 the Telethon raised funds totaling $31 million for 130 participating children's hospitals," said Michele Dodson, Telethon coordinator, Phoenix Children's Hospital.

"This year, Phoenix Children's Hospital will join more than 150 other hospitals for children selected to co-sponsor the Telethon in 170 television markets and in four foreign countries.

**Last year more than $313,000 was pledged to Phoenix Children's Hospital. This was a $100,000 increase over the 1985 Telethon total. Phoenix Children's Hospital plans its Third Annual Children's Miracle Network Telethon.**

A Telethon could not be possible without the help of corporate sponsors. This year's sponsors include: International Dairy Queen, Johnson & Johnson, Kimberly-Clark, General Foods, Heinz U.S.A., Hershey Chocolate Company, Kraft, Marriott Corporation, Nestle Foods, Plough, Inc., Land O'Lakes, Sundor Brands, Stanley Steemer, Golden Corral, and Adventure Land Video.

Marie Osmond, national co-chairman, will preside as host of the national Telethon along with John Schneider, co-founder, national co-chairman. National co-hosts will be Marilyn McCoo and Merlin Olsen. Bob Hope is the Honorary Chairman of the Board of Trustees of the Osmond Foun-

**Continued**

**Telethon, continued**

dation; Jim McMahon is the national Sports Chairman of the Osmond Foundation; and Malcolm-Jamel Warren is the national Youth Chairman.

On the local side, Dave Patterson, anchor for Channel 10, will host the Telethon with the assistance of many members of the Channel 10 News Team.

The Telethon will begin at 6:30 Saturday evening and continue through 4:00 Sunday afternoon. Each hour of the Telethon will include 40 minutes of national entertainment from Disneyland, and 20 minutes of local programming from Channel 10 studios with a live remote from the hospital. ■

**Amy Petrovsky,**
**Phoenix Children's Hospital**

## Flexible Angioscopy vs Arteriography

Flexible, fiberoptic endoscopes are used widely in such fields as gastroenterology and otolaryngology but have not evolved as quickly in angioscopy (imaging blood vessels), reports a study in the March *Archives of Surgery*. However, flexible angioscopy appears to be faster and more specific than arteriography in imaging vessels and grafts in patients undergoing peripheral arterial reconstruction or coronary bypass, the study concludes. Greg Van Stiegmann, M.D., of the University of Colorado Health Sciences Center, Denver, and colleagues performed fiberoptic angioscopy in 25 arteries and grafts in 19 patients. The procedure took three to 10 minutes and resulted in no complications. The researchers say they were able to satisfactorily visualize the vessels and specifically spot previously unsuspected problems using the fiberoptic system.

**MEDI-LOGS**
**are**
**still available.**

**Contact**
**The**
**Arizona Medical**
**Association**

810 W. Bethany Home Rd.
Phoenix, Arizona 85013
246-8901

PHOENIX MANAGEMENT SERVICES INC.

PMS SINCE 1980 THE Collectors

FOR

MEDICAL • RETAIL • COMMERCIAL

LICENSED • BONDED
FAST • COURTEOUS • PROFESSIONAL
NATIONAL & INTERNATIONAL COLLECTIONS

CALL THE PROFESSIONALS
3530 E. INDIAN SCHOOL RD.

956-3459

## The Arizona Medical Association, Inc.
## 1987 ANNUAL MEETING
## The Pointe at South Mountain
## 7777 South Pointe Parkway, Phoenix, Arizona
## SCHEDULE OF EVENTS

### Thursday, June 4, 1987

| | | |
|---|---|---|
| 8 a.m. - 12 noon | **Current Perspectives Program** | |
| | Surgery | Coronado |
| | Internal Medicine | Cortez |
| | Pediatrics | Sonora |
| | Obstetrics & Gynecology | Kachina |
| | Family & Community Medicine | Yucca |
| 9 a.m. - 10:30 a.m. | *Auxiliary Opening Meeting* | Apache |
| 10:30 a.m. - 11:30 a.m. | *Auxiliary Legislation Workshop* | Apache |
| 11:30 a.m. - 1 p.m. | *Auxiliary Luncheon* | West Garden |
| 1 p.m. - 5 p.m. | **Current Perspectives Program** | |
| | Surgery | Coronado |
| | Internal Medicine | Cortez |
| | Emergency Medicine | Sonora |
| | Dermatology | Kachina |
| | Orthopedic Surgery & Sports Medicine | Yucca |
| 1 p.m. - 5 p.m. | Hospital Medical Staff Section | |
| | Program and Annual Meeting | Zuni |
| 1 p.m. - 4 p.m. | Arizona Orthopaedic Society | Palo Verde Room #1 |
| 2 p.m. - 3:30 p.m. | *Auxiliary Reference Committee* | Apache |
| 2 p.m. - 3:30 p.m. | *Auxiliary Reference Committee* | Grand Canyon 1 |
| 2 p.m. - 5 p.m. | Arizona Chapter, American | |
| | College of OB/GYN | Saguaro |
| 3:30 p.m. - 5 p.m. | *Auxiliary House of Delegates* | Apache |
| 7 p.m. | Reception | Rustler's Rooste |
| 8 p.m. | M*A*S*H BASH | Rustler's Rooste |

### Friday, June 5, 1987

| | | |
|---|---|---|
| 6 a.m. - 8 a.m. | Executive Committee Breakfast | #6002 |
| 7:30 a.m. - 8:30 a.m. | *Auxiliary County Caucus* | Apache |
| 8 a.m. - 10 a.m. | Board of Directors | Cortez |
| 8:30 a.m. - 10 a.m. | *Auxiliary House of Delegates* | Apache |
| 10 a.m. - 12 noon | House of Delegates | Pima |
| 11 a.m. - 12 noon | *Auxiliary Workshop* | Apache |
| 12 noon - 4 p.m. | Past Presidents' Luncheon | #6001 |
| 12 noon - 3 p.m. | *Auxiliary Luncheon* | Cortez |
| 2 p.m. - 5 p.m. | Amendments Reference Committee | Pima |
| 2 p.m. - 5 p.m. | Resolutions Reference Committee | Hopi |
| 3 p.m. - 5 p.m. | *Auxiliary Summer Board Meeting* | Apache |
| 7 p.m. | President's Reception | West Garden |
| 8 p.m. | President's Banquet | Cortez/Coronado |

### Saturday, June 6, 1987

| | | |
|---|---|---|
| 6:30 a.m. - 8 a.m. | Maricopa County Caucus | Apache |
| 6:30 a.m. - 8 a.m. | Pima County Caucus | Pima |
| 8 a.m. - 12 noon | House of Delegates | Zuni |
| 12 noon - 3 p.m. | Board of Directors' Luncheon | Navajo |
| 1:30 p.m. - 4:30 p.m. | Young Physicians Section | Hopi |
| 4:30 p.m. - 5:30 p.m. | Young Physicians Section Reception | Grand Canyon 2 |

# Physicians in the News

## Mother of the Year

**Carolyn Gerster, M.D. and Governor Evan Mecham**
Photo by Charles Krejcsi/Arizona Republic/March 13, 1987

Scottsdale internal medicine specialist **Carolyn Gerster, M.D.,** has been named Arizona's 1987 Mother of the Year, the first physician to be the recipient of the honor.

Dr. Gerster received a commemorative plaque, above, from Governor Evan Mecham, was honored by the Arizona State Legislature and was guest of honor at a luncheon sponsored by the Governor's Office of Women's Services. The Mother of the Year program is sponsored by American Mothers, Inc., the official sponsor of Mother's Day and an organization dedicated to "strengthening the moral and spiritual foundation of the family and the home."

Dr. Gerster said her philosophy of parenting is "to create a love that guides the child toward realization of his own potential and nurtures his devotion to God and concern for the helpless." Being a parent, she said, "is a stewardship, not an ownership." Dr. Gerster and her husband, cardiologist Josef Gerster, M.D., have been married 29 years and have five children.

Her civic service includes service as a delegate to the United Nations International Focus on Women Conference in Nairobi, Kenya, in 1985 and as a 1984 delegate to the United Nations International Conference on Population in Mexico City. She has spoken to students on the hazards of smoking; conducted seminars for seniors on hypertension and coronary artery disease; and was active in researching treatments for Valley Fever.

"Reprinted with permission of the *Arizona Republic*. Permission does not imply endorsement by the newspaper."

## Dr. Molthan Honored By Smith College

**Dr. Marian Molthan**

**Dr. Marian Molthan**, director of pediatric cardiology, Phoenix Children's Hospital, was presented with the prestigious Smith College Medal in February in Northhampton, Massachusetts. The award honors Alumnae who best "exemplify in their lives and in service to their communities the true purpose of a liberal arts education."

"I was surprised to receive this notable award," said Dr. Molthan. "It was a wonderful experience to be back at the college for this celebration.

Dr. Molthan, who graduated from Smith in 1949, has been presented with various distin-

**Dr. Molthan, Continued**

guished awards over the years. In 1979, Dr. Molthan received the Joseph Bank Medal by the Maricopa County Medical Society for distinguished public service in recognition of her compassion and concern for the total patient and of her long and dedicated service to children on the Indian Reservations throughout Arizona. In 1982, she received the Sammy Award from Samaritan Health Service in recognition of her commitment and work. She also received the MCH Golden Anniversary Award from the Arizona Department of Health Services in 1985 and the Distinguished Service Award from the Indian Health Service in 1986.

## Solar Sneeze Reflex

A letter in a recent *Journal of the American Medical Association* suggests allergy treatment may also ease "solar sneeze reflex," the common but poorly understood phenomenon of sneezing when entering sunlight, in some patients with both problems. David M. Lang, M.D., and William C. Howland III, M.D., of the Scripps Clinic and Research Foundation, La Jolla, California, studied 138 patients treated for different types of allergic rhinitis, or runny nose; 15 of these also had solar sneeze reflex. Antihistamine, decongestant and other therapy improved the rhinitis, and seven of the 15 also reported improvement in their solar sneezes. Noting other authors have suggested solar sneezes may be a particular problem for baseball outfielders and airplane pilots, the letter notes, "we would add punt return specialists, sky divers and high-wire acrobats, for whom a solar sneeze may be more than just a light matter."

## Dietary Control of Parkinson's Fluctuations

A low-protein daytime diet apparently can help control the crippling movement fluctuations commonly seen in Parkinson's disease patients under prolonged treatment with the widely used drug L-dopa-carbidopa, reports a study in the March *Archives of Neurology*. Jonathan H. Pincus, M.D., and Kathryn Barry, MSN, RN, of the Yale University School of Medicine, New Haven, Connecticut, say 11 Parkinson's patients put on a nearly zero-protein daytime diet demonstrated great sensitivity to L-dopa and reduced fluctuations. The study says the diet allowed a reduction in the patients' total daily L-dopa dose and discontinuation of all adjuvant therapy to control the fluctuations "while the patients maintained a near normal clinical state." At a year's follow-up, all patients were healthy and at or above ideal body weight.

## Brain Metabolism In Obsessive-Compulsive Disorder

Patients with obsessive-compulsive disorder have higher than normal rates of glucose metabolism in certain parts of their brains, says a study in the March *Archives of General Psychiatry*. Lewis R. Baxter, Jr., M.D., of the UCLA School of Medicine, Los Angeles, and colleagues studied 14 obsessive- compulsive patients, using positron emission tomography to gauge glucose metabolism in brain areas thought to function abnormally in this disorder. These patients had significantly higher metabolism in the caudate nucleus, a sort of central switching area for the brain, and an area called the orbital gyrus, which is associated with emotion, than did 14 normal controls and 14 patients with depression. Some abnormalities remained even after successful drug treatment. "Our findings do not address the cause of the disorder," the study concludes, "but rather the neuroanatomic localization of the cerebral glucose metabolic processes that may mediate its expression."

## Prolonged Mechanical Ventilation

It is not uncommon for critically ill patients to require respirators for long periods of time, but little is known about the outcome of mechanical ventilation in patients placed on such devices for more than a few days. A study in the March *Archives of Internal Medicine* finds prolonged mechanical ventilation is associated with limited survival and poor functional status in those who do survive. James E. Spicher, M.D., and David P. White, M.D., of the Pennsylvania State University's Milton S. Hershey Medical Center, Hershey, Pennsylvania, reviewed the medical records of 250 patients who spent at least 10 days on a respirator during a five-year period. Overall survival was 39 percent at discharge, 29 percent at one year and 22.5 percent at two years. Age and functional status prior to respiratory failure were the best predictors of survival, the study says. Of patients who survived to discharge, 40 percent went to nursing homes and 33 percent were confined to their homes.

## Primary Non-Hodgkins Lymphoma of Heart In AIDS

Researchers writing in the March *Archives of Pathology and Laboratory Medicine* describe what may be the first reported cases of primary cardiac lymphoma in AIDS patients. In neither of the two newly reported cases was the malignancy suspected clinically, say Jeannette Guarner, M.D., of the Emory University School of Medicine, Atlanta, and colleagues. There have been multiple reports of non-Hodgkins lymphomas developing in patients with AIDS, primary immunodeficiencies and in transplant patients, the report notes, but "to our knowledge, no cases of primary non-Hodgkins lymphoma of the heart in patients with AIDS have been reported." Primary lymphomas of the heart are extemely rare anyway, the researchers say, accounting for less than 6 percent of primary malignant tumors of the heart and pericardium.

## "Tissue Clay" For Nose Augmentation

A study in the March *Archives of Otolaryngology-Head and Neck Surgery* reports on the use of "tissue clay," a new technique for surgical augmentation and sculpting of the nose. The "clay," a mixture of microfibrillar collagen and a small amount of whole blood from the patient, is prepared before surgery, injected into a subcutaneous pocket in the nose and sculpted into the desired contour, says Michael Evan Sachs, M.D., of New York Medical College and the New York Eye and Ear Infirmary, New York. The clay solidifies after a week and feels similar to bone. Sachs used the technique in 58 patients over four years, reporting no complications and an average resorption rate over a two-to-four-year period of 16 percent. "The esthetic and functional results in 58 patients were deemed excellent, safe and effective," he notes.

## "Goose Step Hematuria"

A weight-lifter practicing an exaggerated form of "power-walking" may have taken this exercise a bit too far, says a letter in a recent *Journal of the American Medical Association*. Harry D. Kerr, M.D., of the Medical College of Wisconsin, describes a 44-year-old man who sought advice about an episode of painless, dark red urination. The. man said this occurred after he helped push a car out of a snowbank, then walked home—a three-mile distance—by "power-walking." He described this as "similar to goose-step marching," with fully straightened arms swinging forward 90 degrees in synch with a long stiff-legged gait, hips flexed high. This transmits most of the impact of the walking from the heels to the back, Kerr writes. The man began power-walking at the advice of fellow weight-lifters but seems to have considerably exaggerated the technique, which is advocated by body-builder Steve Reeves, Kerr says. "Sometimes 'walking' may not be just walking," he concludes.

## Vegetarian Thermodynamics

The reduced energy expenditure and intake noted in vegetarians may be a result of their high-fiber diet, which is rich in unrefined carbohydrates, vegetables and fruits, a letter in a recent *Journal of the American Medical Association* suggests. Franco Contaldo, M.D., and Alberto Coltorti, of the University of Naples, Italy, studied the effect of dietary fiber on post-meal thermogenesis (heat production in the body) in seven subjects, finding significantly more heat was produced after a low-fiber meal than after one high in fiber content. "Our study suggests that dietary fiber may affect not only energy intake (through the well-known satiety effect) but also energy expenditure," they say. "These findings may contribute to the understanding of low energy requirements (and therefore low energy intake) in vegetarians compared with individuals on the usual mixed American or European diet."

ARIZONA PHYSICIANS' DIRECTORY

Announcing a
Practice?
Relocating?
New Physician?

Block space is available in *Arizona Medicine* for advising member physicians.

Two-month minimum. Payment must accompany order.

Members — $20 per month
Nonmembers — $30 per month

# MAGAZINE SUBSCRIPTIONS AT HUGE SAVINGS

## ARIZONA MEDICAL ASSOCIATION MAGAZINE PROGRAM

*a division of Subscription Services, Inc.*

**29 Glen Cove Avenue • Glen Cove, New York 11542 • 516-676-4300**

Our members qualify for low professional subscription rates for magazines for office reception room use. In addition, many members are educators associated with universities or teaching hospitals and may order magazines at special educator rates. If you wish to select any educator rates, be sure to complete the section of the coupon that requests your affiliated institution. Please note that our list contains the prices in both categories. You may renew or extend your present subscription through the program.

| PUBLICATION | (No. of issues per yr.) | REG SUBSCR. PRICE | YOUR OFFICE PRICE | YOUR EDUC. PRICE |
|---|---|---|---|---|
| American Health | 10 | 14.95 | 12.95 | 11.95 |
| American Heritage | 6 | 24.00 | 18.00 | 18.00 |
| Amer.Photog.[Special:8 iss.] | | 5.98 | | 5.98 |
| Americana | 6 | 11.95 | 11.95 | 9.95 |
| ArtNews | 12 | 29.95 | 25.95 | 25.95 |
| Atlantic Monthly | 12 | 9.95 | 9.95 | 9.95 |
| Audio | 12 | 19.94 | 9.97 | 9.97 |
| AUTOMOBILE | 12 | 18.00 | 9.00 | 11.95 |
| Baseball Digest | 12 | 14.95 | 9.97 | 9.97 |
| Basketball Digest | 8 | 9.95 | 7.97 | 7.97 |
| *Better Homes&Gdns | 12 | 14.00 | 7.00 | 14.00 |
| *BICYCLING | 10 | 15.97 | 8.00 | 12.97 |
| Black Enterprise | 12 | 15.00 | 15.00 | 11.95 |
| Boating | 12 | 21.94 | 18.97 | 18.97 |
| Bon Appetit | 12 | 15.00 | 15.00 | 15.00 |
| Bowling Digest | 6 | 12.00 | 9.97 | 9.97 |
| BULLETIN HIST/MED | 4 | 24.00 | 22.00 | 22.00 |
| Car & Driver | 12 | 16.98 | 11.99 | 11.99 |
| child (Fashion) | 6 | 12.00 | 10.00 | 10.00 |
| Changing Times | 12 | 15.00 | 9.97 | 9.97 |
| *Connoisseur | 12 | 19.95 | 10.00 | 19.95 |
| Consumers Reports | 12 | 16.00 | 16.00 | 16.00 |
| *Cosmopolitan | 12 | 24.97 | 15.00 | 24.97 |
| Cruise Travel | 6 | 12.00 | 9.97 | 9.97 |
| Cycle | 12 | 13.98 | 6.99 | 6.99 |
| Cycle World | 12 | 13.94 | 6.97 | 6.97 |
| DISCOVER | 12 | 23.95 | 14.95 | 14.95 |
| Dog Fancy | 12 | 17.97 | 17.97 | 12.97 |
| EBONY | 12 | 16.00 | 9.97 | 9.97 |
| The Economist | 52 | 85.00 | 51.00 | 51.00 |
| *ELLE | 12 | 24.00 | 16.00 | |
| EM (Ebony Man) | 12 | 24.00 | 19.95 | 19.95 |
| ESQUIRE | 12 | 17.94 | 9.95 | 9.95 |
| Essence | 12 | 12.00 | 9.96 | 9.00 |
| EUROPEAN TRAVEL & LIFE | 10 | 24.00 | 12.00 | 16.00 |
| Family Circle | 17 | 14.97 | 9.97 | |
| Family Computing | 12 | 19.97 | 9.99 | 9.99 |
| Family Handyman | 10 | 9.95 | 9.95 | 5.95 |
| Field & Stream | 12 | 15.94 | 7.97 | 7.97 |
| Fifty Plus | 12 | 15.00 | 11.97 | 11.97 |
| Financial World | 26 | 41.95 | 24.94 | |
| Flying | 12 | 18.98 | 15.97 | 15.97 |
| Food and Wine | 12 | 20.00 | 10.00 | 15.00 |
| Football Digest | 10 | 12.95 | 12.95 | 7.97 |
| Forbes | 28 | 45.00 | 45.00 | 29.95 |
| Fortune | 26 | 44.50 | 35.30 | 22.75 |
| Games Magazine | 12 | 15.97 | 15.97 | 15.97 |
| Gentlemens Quartly | 12 | 18.00 | 13.50 | |
| Glamour | 12 | 15.00 | 12.00 | |
| Golf Digest | 12 | 19.94 | 11.98 | 11.98 |
| Golf Illustrated | 10 | 15.00 | 7.97 | 7.97 |
| Golf Magazine | 12 | 15.94 | 9.97 | 9.97 |
| *Good Housekeeping | 12 | 15.97 | 9.97 | 15.97 |
| Gourmet | 12 | 18.00 | 13.50 | 15.00 |

| PUBLICATION | (No. of issues per yr.) | REG. SUBSCR. PRICE | YOUR OFFICE PRICE | YOUR EDUC. PRICE |
|---|---|---|---|---|
| *Harpers Bazaar | 12 | 16.97 | 8.97 | 16.97 |
| Harpers Magazine | 12 | 18.00 | 9.97 | 9.97 |
| Health [Special:9 issues] | | | 8.97 | 8.97 |
| High Fidelity | 12 | 13.95 | 6.98 | 6.98 |
| Hockey Digest | 8 | 9.95 | 7.97 | 7.97 |
| Home Mechanix | 12 | 11.94 | 8.97 | 8.97 |
| The Homeowner[Special:6 iss] | | | 8.97 | 8.97 |
| Home Viewer | 12 | 18.00 | 11.97 | 11.97 |
| Hot Rod | 12 | 13.94 | 8.97 | 8.97 |
| House and Garden | 12 | 24.00 | 18.00 | |
| *House Beautiful | 12 | 15.97 | 7.99 | 15.97 |
| Inc. | 12 | 24.00 | 12.00 | 12.00 |
| Inside Sports | 12 | 18.00 | 11.97 | 11.97 |
| Jerusalem Post | 24 | 18.46 | 18.46 | 15.97 |
| Jet | 52 | 36.00 | 26.00 | 26.00 |
| Ladies' Home Journal | 12 | 19.95 | 11.97 | 9.98 |
| LITERATURE & MED. | 1 | 12.95 | 10.95 | 10.95 |
| LIFE | 12 | 32.50 | 16.25 | |
| M (Civilized Man) | 12 | 24.00 | 19.95 | |
| Mademoiselle | 12 | 15.00 | 12.00 | |
| McCalls | 12 | 11.95 | 7.95 | |
| METROPOLITAN HOME | 12 | 18.00 | 9.00 | 9.00 |
| Modern Photography | 12 | 13.98 | 7.98 | 6.99 |
| Money | 12 | 34.95 | 16.00 | 15.99 |
| Mother Jones | 12 | 24.00 | 16.00 | 16.00 |
| Motor Trend | 12 | 13.94 | 7.97 | 7.97 |
| MS Magazine | 12 | 16.00 | 10.97 | 10.97 |
| Nation's Business | 12 | 22.00 | 12.97 | 12.97 |
| N.E.Journal of Med. | 52 | | 66.00 | |
| New Republic | 48 | 56.00 | 56.00 | 28.00 |
| New Woman | 12 | 15.00 | 9.95 | 11.97 |
| New Yorker | 52 | 32.00 | 32.00 | 20.00 |
| New York | 50 | 33.00 | 16.50 | 19.98 |
| *NEWSWEEK | 52 | 41.00 | 20.80 | 21.80 |
| OMNI | 12 | 24.00 | 15.96 | 15.96 |
| 1001 Home Ideas[Spec'l:8 iss] | | 11.97 | | 11.97 |
| Organic Gardening | 12 | 12.97 | 11.97 | 11.97 |
| Outdoor Life | 12 | 13.94 | 7.97 | 7.97 |
| Outside | 10 | 16.00 | 12.00 | 8.97 |
| Ovation | 12 | 18.00 | 10.00 | 10.00 |
| PARENTING | 10 | 18.00 | 9.00 | |
| Parents | 12 | 18.00 | 9.00 | 11.95 |
| Penthouse | 12 | 36.00 | 30.00 | 30.00 |
| People | 52 | 56.00 | 56.00 | 30.95 |
| Personal Computing | 12 | 18.00 | 18.00 | 11.97 |
| Petersens Photgrph | 12 | 13.94 | 6.97 | 6.97 |
| Playboy | 12 | 25.00 | 19.00 | 19.00 |
| *Popular Mechanics | 12 | 13.97 | 7.00 | 13.97 |

| PUBLICATION | (No. of issues per yr.) | REG. SUBSCR. PRICE | YOUR OFFICE PRICE | YOUR EDUC. PRICE |
|---|---|---|---|---|
| Popular Photogrphy | 12 | 11.97 | 6.99 | 6.99 |
| Popular Science | 12 | 13.94 | 7.97 | 7.97 |
| *PRACTICAL HOMEOWNER | 9 | 12.97 | 6.50 | 9.97 |
| *PREVENTION | 12 | 13.97 | 7.00 | 13.97 |
| PSYCHOLOGY TODAY | 12 | 15.99 | 8.00 | 8.00 |
| Reader's Digest | 12 | 15.41 | 15.41 | 15.41 |
| *Redbook | 12 | 11.97 | 6.97 | |
| Road and Track | 12 | 19.94 | 14.99 | 14.99 |
| Robb Report | 12 | 65.00 | 65.00 | |
| *RUNNER'S WORLD | 12 | 19.95 | 10.00 | 12.97 |
| Sail | 12 | 21.75 | 21.75 | 21.75 |
| SAILING WORLD | 12 | 21.75 | 10.88 | 10.88 |
| Saturday Eve. Post | 9 | 12.97 | 12.97 | 12.97 |
| Savvy | 12 | 18.00 | 9.00 | 9.00 |
| Self | 12 | 15.00 | 12.00 | |
| Seventeen | 12 | 13.95 | 13.95 | 13.95 |
| Ski | 8 | 11.94 | 6.97 | 6.97 |
| Skiing | 7 | 9.98 | 5.97 | 5.97 |
| Skin Diver | 12 | 13.94 | 7.97 | 7.97 |
| SPORT | 12 | 12.00 | 7.97 | 7.97 |
| Sporting News | 55 | 55.95 | 29.97 | |
| *Sports Afield | 12 | 13.97 | 6.99 | 13.97 |
| SPORTS ILLUSTRATED | 54 | 58.80 | 34.00 | 29.45 |
| Stereo Review | 12 | 9.98 | 4.99 | 4.99 |
| Sunset | 12 | 14.00 | 11.20 | |
| S.Porters Pers.Fin. | 12 | 19.97 | 11.97 | |
| TAXI (Fashion) | 12 | 24.00 | 17.97 | 17.97 |
| Teen | 12 | 12.95 | 7.95 | 7.95 |
| Tennis | 12 | 17.94 | 8.97 | 8.97 |
| TIME | 52 | 58.25 | 29.25 | 29.12 |
| *Town & Country | 12 | 24.00 | 12.00 | 24.00 |
| Travel & Leisure | 12 | 25.00 | 12.50 | 18.00 |
| TV Guide | 52 | 31.20 | 29.90 | 26.00 |
| UNIQUE HOMES | 6 | 29.97 | 19.97 | 19.97 |
| USA Today | 260 | 130.00 | 91.00 | 86.95 |
| U.S.News & World Report | 52 | 34.50 | 17.25 | 17.25 |
| US Magazine | 26 | 23.95 | 12.98 | 12.98 |
| Vegetarian Times | 12 | 19.95 | 14.95 | 14.95 |
| Video | 13 | 12.00 | 8.97 | 8.97 |
| Video Review | 12 | 12.00 | 6.97 | 6.97 |
| Vogue | 12 | 24.00 | 21.00 | |
| W Magazine | 26 | 26.00 | 23.00 | 17.95 |
| Weight Watchers | 12 | 13.97 | 11.97 | 11.97 |
| Woman's Day | 17 | 16.97 | 16.97 | 16.97 |
| Women's Sports | 12 | 12.95 | 7.97 | 8.95 |
| WORKING MOTHER | 12 | 11.95 | 7.95 | |
| Working Woman | 12 | 18.00 | 12.00 | 15.00 |
| World Tennis[Special:6 issues] | | 5.97 | | 5.97 |
| WORLD TRAVELING | 4 | 11.00 | 9.95 | 9.95 |
| YM | 12 | 14.00 | 7.00 | 10.95 |

* BUSINESS CARD NEEDED FOR OFFICE PRICE

**ArMA MAGAZINE PROGRAM**
**29 Glen Cove Avenue**
**Glen Cove, New York 11542**

NAME _____

ADDRESS _____

CITY _____ STATE _____ ZIP _____

Complete for Educator rates:

_____ _____
Name of Educator Affiliated Hospital / School

☐ VISA
☐ M/C No. _____ Exp. Date _____

You may pay by check or credit card. Please make checks payable to ArMA Magazine Program.

| NAME OF PUBLICATION | YEARS | PRICE |
|---|---|---|
| | | |
| | | |
| | | |
| | | |
| | | |
| | TOTAL | |

Terms: Subscriptions are one year unless otherwise noted. Prices subject to publishers' changes.
Guarantee: Our prices are the lowest, our service the best.
Renewals: Please send the address label from your magazine at least 8 weeks in advance of expiration date.
New Orders: Publishers take from 8 to 12 weeks to start your subscription.

AZMD287

# Classified Advertising


**We Bind Your**
**PERIODICALS**

Preserve your medical journals as beautifully bound books. Choose from 30 different colors of durable Library Buckram.

**$14.50 per volume, (name imprint $1.00)**
**$15.50 Imitation Leather, (rules .50 each)**

Inquire about quantity discounts. **Free** local pickup and delivery on 10 volumes or more. Minimum order is $25.00.

**ROSWELL BOOKBINDING**
**2614 North 29th Avenue**
**Phoenix, Arizona 85009 ■ (602) 272-9338**

P A S

*"People, The Reason And The Key"*

**Personnel Administration Services, Inc.**
3080 North Civic Center, Suites 11 & 12
Scottsdale, Arizona 85251

(602) 947-8053
(602) 947-8375

**EDWARD N. PHILLIPS**
President

**IMMEDIATE CASH**
We Will Fund Your
Medical Insurance Receivables
**NOW**
Our Service Will Solve Your
CASH-FLOW Concerns

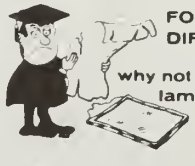
Call Kevin at "the MONEY COMPANY"
(602) 968-3747

**DANNY T. SEIVERT**
**INSURANCE, INC.**
Professional Programs
for Professional People
**70 E. Mitchell Dr., Suite 6**
**Phoenix, Arizona 85012**
**263-9090**

**MEDICAL SPACE AVAILABLE**
**at the**
**PROFESSIONAL CENTER**
2610 West Bethany Home Road (At I-17)

Managed by
Public Management & Appraisal
(602) 249-9072

YOU WORKED HARD




It will last a lifetime....
**THE PLAQUE SHOP**

Wood ploques — Reody to hong
No gloss to breok — Moisture proof
Dirt proof — Impressive.
Our ploques ore monufoctured locolly.

**ARIZONA LAMINATING SERVICE, INC.**
**7231 East First Avenue**
**Scottsdale, Arizona 85251**
**(602) 945-9338**

## PROFESSIONAL OPPORTUNITIES

### INTERNIST

with an interest in Gastroenterology needed to join a Cardiologist/Internist in a rural Louisiana town from July, 1987. Attractive first year salary, benefits, and early partnership. If interested, send C.V. to: Manzoor H. Qazi, M.D., 1101A Port Arthur Terrace, Leesville, LA 71446.

### RADIOLOGIST

Board Certified, seeking to relocate, University trained, extensive experience all phases of radiology including administration and teaching. Arizona license — interested Tucson area. Write Arizona Medical Association, P.O. Box 40687, Phoenix, Arizona 85013.

### ARIZONA FAMILY PRACTICE—BC/BE

For rapidly expanding practice. Early shareholder. Bilingual is important. Submit CV to: 809 E. Washington #105, Phoenix, Arizona 85034.

### MEDICAL PRACTICE SALES AND APPRAISALS

We specialize in the valuation and selling of medical practices. If interested in buying or selling a medical practice, contact our Brokerage Division at The Health Care Group, 400 GSB Building, Bala Cynwyd, PA 19004; (215) 667-8630.

### FAMILY PRACTICE

To do family care in multi-specialty clinic and satellite clinic. Full in-house lab and x-ray. Delightful community, good schools and recreation. Reply to: P.O. Box 0955, C/O Arizona Medicine, 810 West Bethany Home Road, Phoenix, Arizona 85013.

## MEDICAL OFFICES

### OFFICES FOR LEASE

1840 E. Baseline, Tempe, Arizona (East of McClintock) close to Hospitals, 1/2 mile from Superstition Freeway, lush landscaping, competitive rates with free rent, excellent parking and access. Contact Michael Beall, **L.J. Hooker International** (602) 956-5250.

### OFFICE SPACE

**Scottsdale office for lease:** Excellent, **New** 2000 ft., prof. designed, includes two Private Offices, Recpt. Rm., Admn./Accounting, two Prep Rms., 4 Exam Rms., Lab and two toilets. 7330 East Earll Dr., just off Civic Plaza. Call Art Kappelmann, **The Westwind Company** — (602) 945-4071.

### MEDICAL OFFICE TO RENT

1500 Sq. feet Modern office space in Paradise Valley, AZ (Phoenix), available July 1, 1987. Ideal for Family Practice, Specialists, near 2 major hospitals. Reply: 3326 E. Sweetwater, Phoenix, Arizona 85032.

## MISCELLANEOUS

### FAST GROWING NATION-WIDE FRANCHISE

Sale and Delivery of Teddy Bears — All occasions. For Sale: Mesa Store & Franchise. Perfect for family, 2nd income or woman's start-up business. Call owner (eves.) (712) 225-2131. Est. investment — $50,000.

### LARGE LOANS

Since 1966 specializing in large loans to physicians nationwide from $15,000.00 to $90,000.00. Long repayment terms at fixed interest rates. Commitments usually within 48 hours. Woodside Capital Corp., Woodside Capital Building, P.O. Box 368, Woodland Hills, CA 91365. For further information call (800) 423-5025.

### PHYSICIANS SIGNATURE LOANS

Loans to $50,000. Competitive fixed rates. No collateral. Up to seven years to repay with no pre-payment penalties. Prompt, courteous service. Physicians Service Association, Atlanta, Georgia (800) 241-6905. Serving MDs for over ten years.

*Classified ad rates are $20 for the first 50 words or less and 20 cents for each additional word. Send to: ArMA, 810 West Bethany Home Road, Phoenix, Arizona 85013.*


# WHY AMA?

Today you can have instant access to a broad range of up-to-the-minute clinical information and protocols for use in patient care through the Medical Information Network. This nationwide, computerized system was developed by the AMA, with General Telephone and Electronics (GTE), to provide you with the most advanced, current scientific information. It's one more good reason why you should be a part of the AMA.

**To Join,**
Contact your county or state medical society or write: Division of Membership, AMA, 535 North Dearborn Street, Chicago, Illinois 60610 or call collect, (312) 751-6196.

# Clinical Investigation

# Serum Potassium Concentration in Hyperglycemia of Diabetes Mellitus With Long-term Dialysis

ANTONIOS H. TZAMALOUKAS, MD, *and* PRATAP S. AVASTHI, MD, *Albuquerque*

*Severe hyperkalemia (serum potassium level >6 mmol per liter [mEq per liter]), often with electrocardiographic disturbances, was noted at presentation in 30% of 73 hyperglycemic episodes (serum glucose concentration >25 mmol per liter [455 mg per dl]) observed in 15 in-hospital patients with insulin-dependent diabetes mellitus who were receiving long-term hemodialysis or peritoneal dialysis. Serum glucose concentration and total carbon dioxide content correlated significantly with the presenting serum potassium concentration. Treatment with parenteral insulin alone resulted in a decrease of the serum glucose value from 41 ± 14 (standard deviation) to 11 ± 5 mmol per liter (P <.001) and of serum potassium level from 5.2 ± 1.2 to 4.0 ± 0.6 mmol per liter (P <.001). The changes in serum glucose concentration and in carbon dioxide content and the serum potassium concentration at hyperglycemia were found to be independent correlates of the decrease in potassium concentration during treatment. Insulin alone resulted in correction of hyperkalemia in all instances. Posttreatment hypokalemia was noted in only two instances, each associated with both ketoacidosis and low-normal serum potassium concentration at hyperglycemia. Giving insulin is the only treatment usually needed for the hyperkalemia of hyperglycemia in patients on ongoing dialysis.*

(Tzamaloukas AH, Avasthi PS: Serum potassium concentration in hyperglycemia of diabetes mellitus with long-term dialysis. West J Med 1987 May; 146:571-575)

Lethal hyperkalemia has been reported with severe hyperglycemia in patients receiving ongoing dialysis.[1,2] The incidence, the association with the other laboratory abnormalities of hyperglycemia and the management of hyperkalemia in this syndrome have not been studied in detail, however. Administration of only insulin was reported to be adequate treatment for serum potassium abnormalities in cases of severe hyperglycemia of patients receiving long-term dialysis if acid-base balance does not change during treatment.[3]

We studied the serum potassium concentration in a large number of hyperglycemic episodes in dialysis patients. In this report we address the following questions: What are the frequency and clinical importance of serum potassium abnormalities? Which of the biochemical variables known to influence internal potassium balance[4] are statistically related to serum potassium concentration and to its changes during treatment of hyperglycemia of dialysis? Finally, the major issue addressed was whether or not giving only insulin is adequate treatment for elevated serum potassium concentration with or without acid-base balance changes.

## Patients and Methods

We studied 15 patients with insulin-dependent diabetes mellitus (2 women, 13 men) on long-term dialysis therapy (hemodialysis 5, continuous ambulatory peritoneal dialysis [CAPD] 9, intermittent peritoneal dialysis [IPD] 1) who had hyperglycemia (serum glucose level >25 mmol per liter)* on admission or in whom hyperglycemia developed in the hospital. The 73 hyperglycemic episodes observed (1 to 11 per patient) developed 12 to 48 hours after dialysis in patients receiving hemodialysis and during dialysis in patients receiving CAPD or IPD. During treatment, dialysis was discontinued and insulin (2 to 5 units per hour) was administered either by continuous intravenous infusion or by frequent (every one to two hours) injections. All patients had oliguria, none had fluid losses through vomiting or diarrhea and none received fluid or base during treatment (the study period). Insulin administration was discontinued when the serum glucose concentration approached 10 to 15 mmol per liter. The study period lasted 8 to 25 hours.

Tonicity was computed as twice the serum sodium concentration, plus glucose concentration, in millimoles per liter.[5,6] Results are reported as range (mean ± standard deviation). The initial serum potassium concentration and change in serum potassium levels were compared with the other biochemical variables by correlation, analysis of variance and multiple linear regression, performed by Dorothy Pathak, PhD. We compared the initial with final biochemical measurements by the paired *t* test and episodes that included ketoacidosis with episodes without ketoacidosis by the nonpaired *t* test. The change in potassium value divided by the change in glucose value was compared with the initial serum potassium concentration by correlation and linear regression.[3]

*SI units (Système International d'Unités) are given throughout this article for serum glucose and potassium concentrations. The factor to convert glucose values to conventional units (mg per dl) is 0.055. To convert potassium values to the conventional milliequivalents per liter, the factor is 1.

From the Division of Nephrology, Department of Medicine, Veterans Administration Medical Center and University of New Mexico School of Medicine, Albuquerque. Reprint requests to Antonios H. Tzamaloukas, MD, Renal Section (111C), Veterans Administration Medical Center, 2100 Ridgecrest Dr, SE, Albuquerque, NM 87108.

ABBREVIATIONS USED IN TEXT

CAPD = continuous ambulatory peritoneal dialysis
IPD = intermittent peritoneal dialysis
$Paco_2$ = partial pressure of arterial carbon dioxide

## Results

Clinical presentation, frequency and degree of hyperglycemia, other biochemical measurements and outcome were similar in this study, regardless of the method of dialysis. Therefore, all hyperglycemic episodes (16 following hemodialysis, 49 during CAPD and 8 during IPD) are reported together.

Hyperglycemia usually developed in patients with severe illnesses. Seven patients had cardiac disease (acute myocardial infarction, severe congestive heart failure). Five other patients had infections—two urinary tract infections, one sepsis from leg gangrene, one sepsis from a clotted and infected bovine arteriovenous graft and one peritonitis. In four patients, hyperglycemia was related to compliance problems. In nine episodes, ketoacidosis was also present.

The most common presenting complaint was intense thirst. Dyspnea and abdominal pain temporally related to ketoacidosis disappeared with its correction. Dyspnea with radiographic findings of pulmonary edema was observed in seven other episodes and abated with correction of hyperglycemia. Neurologic manifestations, from lethargy to coma, developed during the episodes with ketoacidosis and during ten episodes in the two patients with sepsis. One of the septic patients also had a grand mal seizure (serum glucose concentration 65 mmol per liter, tonicity 321 mosm per liter). Other presenting complaints included nausea, vomiting and leg cramps. With treatment, hyperglycemic symptoms were lessened or disappeared in all patients. Seven patients, however, died days or weeks later, during the same hospital admission, of sepsis (two patients) or cardiac causes.

The serum potassium concentration at hyperglycemia (Figure 1) was below normal in 1%, in the normal range in 52% and above normal in 47% of the episodes (>6 mmol per liter in 30%). To study whether hyperkalemia was truly associated with hyperglycemia, we compared serum potassium levels at hyperglycemia with those at euglycemia (glucose 6.1 ±0.9 mmol per liter). The potassium level at euglycemia (2 to 15 specimens per patient) did not include posttreatment values, up to 24 hours, but included all potassium values of blood specimens with glucose levels of less than 10 mmol per liter that were obtained during the same admission. The serum potassium concentration at euglycemia was (2.6 to 5.1, 4.1 ± 0.2 mmol per liter) less than the serum potassium value at hyperglycemia ($P < .001$, paired $t$ test). Electrocardiograms were taken during several episodes and showed hyperkalemic changes frequently at serum potassium levels of greater than 6 mmol per liter, but rarely below this value. The return of the potassium towards normal levels after insulin administration resulted in disappearance of the electrocardiographic findings of hyperkalemia. In several patients, continuous electrocardiographic monitoring throughout treatment showed no life-threatening dysrhythmia.

Table 1 shows initial (at hyperglycemia) and final (posttreatment) biochemical variables, their changes during treatment and the statistical analysis. The serum potassium concentration did not change in two episodes (at 3.0 and 3.8 mmol per liter, respectively) and increased in three other episodes (3.8 to 4.1, 3.9 to 4.1 and 3.9 to 4.3 mmol per liter). A decrease in the carbon dioxide content during treatment (26 to 18 mmol per liter) was noted in the last episode. The initial potassium correlated significantly with the initial glucose, tonicity, $CO_2$ and arterial partial pressure of carbon dioxide ($Paco_2$). Figure 2 shows the relation between the initial potassium concentration and $CO_2$ content as an example of significant correlation. The mean potassium was progressively higher at progressively lower intervals of $CO_2$ content. Individual serum potassium values, however, varied greatly within the same interval of serum $CO_2$. By multiple regression, the combined initial glucose level, tonicity, $CO_2$ content, pH and $Paco_2$ accounted statistically for .278 ($r^2$) of the variability in the initial serum potassium level (Table 1). By

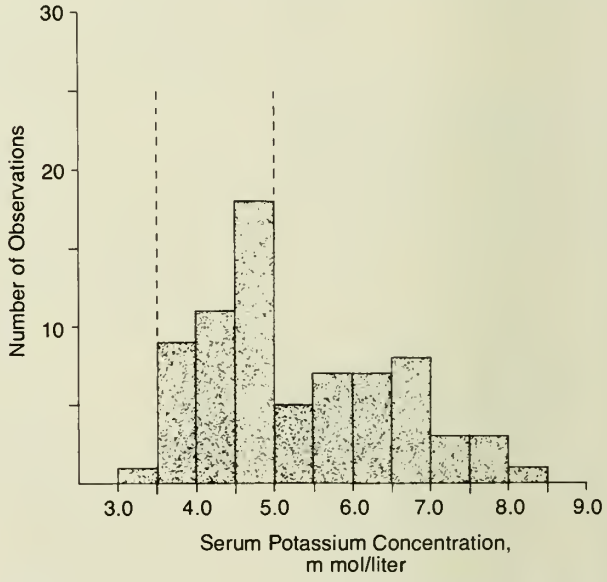



**Figure 1.**—The graph shows distribution of presenting serum potassium concentration in 73 hyperglycemic episodes in patients with insulin-dependent diabetes mellitus receiving ongoing dialysis. Interrupted lines indicate lower and upper normal limits.

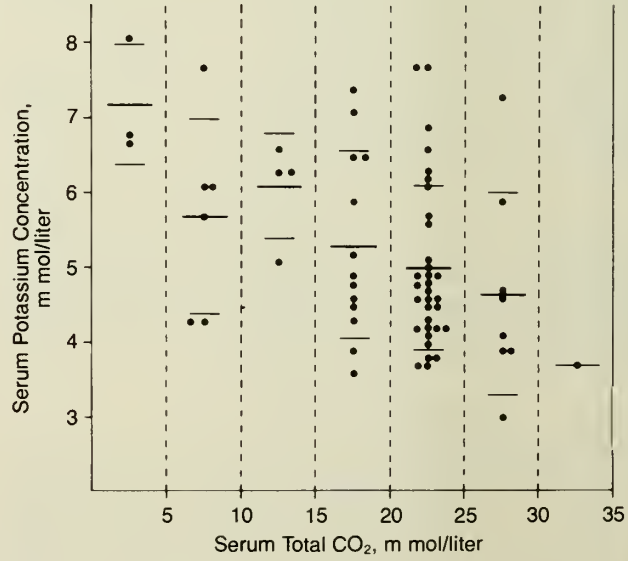



**Figure 2.**—The graph shows comparison of initial serum potassium concentration to initial serum carbon dioxide content in patients with hyperglycemia due to dialysis. Analysis of variance was significant ($P < .05$). Mean potassium levels (thicker horizontal lines) are higher at lower total $CO_2$ intervals. Within each 5 mmol per liter total $CO_2$ interval, however, the standard deviation (thinner horizontal lines) and the range of serum potassium levels were great.

TABLE 1.—*Initial and Final Biochemical Variables in Hyperglycemia of Dialysis*

| *Concentrations in Serum* | *Potassium, mmol/liter* | *Glucose, mmol/liter* | *Tonicity, mosm/liter* | *Total $CO_2$ mmol/liter* | *Arterial pH* | *Arterial $Pco_2$, torr* |
|---|---|---|---|---|---|---|
| Initial, range | 3.0 to 8.1 | 25 to 81 | 268 to 321 | 2 to 31 | 6.79 to 7.51 | 12.0 to 66.0 |
| Mean±SD | 5.2±1.2 | 41±14 | 293±11 | 20±7 | 7.32±0.17 | 30.4±11.6 |
| *r** | ... | .428 | .246 | −.428 | −.187 | −.378 |
| *P*† | ... | .0002 | .04 | .0003 | NS | .02 |
| Final, range | 2.4 to 5.6 | 2 to 25 | 253 to 300 | 16 to 33 | 7.32 to 7.70 | 14 to 40 |
| Mean±SD | 4.0±0.6 | 11±5 | 279±9 | 24±4 | 7.46±0.11 | 33.5±11.0 |
| *P*‡ | <.001 | <.001 | <.001 | <.001 | NS | NS |
| Change, range | −4.0 to +0.4 | −12 to −70 | −4 to −36 | −8 to +17 | −0.06 to +0.55 | −26 to +26 |
| Mean±SD | −1.2±0.4 | −30±13 | −14±7 | +4±6 | +0.14±0.13 | +3.1±11.7 |
| *r** | −.850 | ... | ... | ... | ... | ... |
| *r*§ | | .663 | .654 | −.619 | −.472 | −.574 |
| *P*† | .0001 | .0001 | .0001 | .0001 | .007 | .0007 |
| N | 73 | 73 | 69 | 68 | 37 | 37 |

NS=no significance, $Pco_2$=partial pressure of carbon dioxide, SD=standard deviation

*Correlation with initial serum potassium level.
†Significance of correlation.
‡Significance of the difference between initial and final values.
§Correlation with the change in potassium concentration.

stepwise regression, only the initial serum glucose value and $CO_2$ content met the .150 significance level for entry into the statistical model. Combined initial serum glucose concentrations and $CO_2$ content accounted for .239 of the statistical variability in the initial serum potassium level.

The change in potassium level correlated significantly with the initial potassium and with the change in each of the other biochemical variables (Table 1). By multiple regression, the combined changes in all the other measurements accounted statistically for .555 of the variability in the change in potassium level. By stepwise regression, the change in serum glucose and $CO_2$ content met the .150 significance level and combined accounted for .488 of the statistical variability of the change in potassium. The initial potassium, change in serum glucose and change in $CO_2$ content accounted statistically for .891 of the variability in the change in potassium value. The effect of the initial potassium concentration on the change in serum potassium was independent of the effects of the other variables. Comparison of the change in potassium value per the change in glucose to the initial serum potassium ($x$ axis) revealed $y = -0.060 + 0.019x$, $r = .807$ ($P < .0001$).

For the nine episodes of ketoacidosis, the initial potassium ($5.9 \pm 1.2$ mmol per liter), glucose ($56 \pm 19$ mmol per liter) and tonicity ($301 \pm 15$ mosm per liter) did not statistically differ from the corresponding values of the 64 episodes without ketoacidosis; the initial $CO_2$ content ($6 \pm 3$ mmol per liter), arterial blood pH ($7.08 \pm 0.14$) and $Paco_2$ ($16 \pm 6$ torr) were all statistically less than the corresponding values for the episodes without ketoacidosis. For the episodes with ketoacidosis, the initial potassium value did not correlate with any of the other initial variables. The final potassium ($3.7 \pm 0.7$ mmol per liter) and change in serum potassium ($-2.2 \pm 0.9$ mmol per liter) did not differ statistically from the corresponding values of the episodes without ketoacidosis. The change in potassium concentration correlated only with the initial potassium level ($r = .776$, $P = .014$) and marginally with the change in glucose ($r = .647$, $P = .059$). For ketoacidosis episodes, the change in the potassium concentration per the change in pH was $-0.5$ to $-1.8$ ($-0.9 \pm 0.5$) mmol per liter per 0.1 unit.

Potassium replacement (20 and 10 mmol of potassium chloride given intravenously, respectively) was needed after the end of the study for only two patients with both ketoacidosis and protracted vomiting before presentation. The initial potassium concentration was 4.1 and 3.9 mmol per liter, respectively; the serum potassium level at the end of the study was 2.4 and 2.5 mmol per liter, respectively, for these patients.

## Discussion

Patients with diabetes mellitus in whom hyperglycemia develops are at risk of hyperkalemia, even in the absence of acidosis[7-14] and even when serum aldosterone levels are normal.[15] The increased urinary excretion of potassium,[16] however, prevents severe hyperkalemia in hyperglycemic patients with intact renal function. Usually only patients with impaired renal function have severe hyperkalemia from hyperglycemia without acidosis.[8]

Diabetic patients on dialysis therapy have severely impaired renal function and are reportedly at risk of lethal hyperkalemia from hyperglycemia.[1,2] The serum potassium level, however, was in the normal range in most published reports of dialysis hyperglycemia.[17-22] In the present report, patients had normal potassium levels at euglycemia and were not receiving hyperkalemic medications. Severe hyperkalemia with electrocardiographic abnormalities, but no mortality, was found during 30% of the hyperglycemic episodes. Catabolic diseases were associated with the hyperglycemic episodes in these patients. The frequency of hyperkalemia at hyperglycemia was high, whether the patients were receiving hemodialysis or CAPD. In contrast, in routine outpatient measurements in diabetic patients, including the 15 patients of this study, we frequently found severe hyperkalemia with hyperglycemia before hemodialysis (39% of 59 episodes), but only occasionally with hyperglycemia observed in patients on CAPD therapy.[23] Kaldany and co-workers reported a 50% frequency of severe hyperkalemia in eight hyperglycemic episodes in patients receiving hemodialysis.[24]

Pathogenetically, the potential mechanisms of hyperkalemia with hyperglycemia include hypertonicity, metabolic acidosis and insulin deficiency. In hypertonicity, shifts of

intracellular potassium into the extracellular compartment[25] are independent of acid-base changes[26] and may create severe hyperkalemia at hyperglycemia.[27] Hypertonicity is usually not severe in episodes of hyperglycemia of patients receiving dialysis.[22,28] Consequently, the hyperkalemic effect of hypertonicity is usually minor in these patients. An increased blood urea nitrogen concentration creates hyperosmolality in renal failure[5] but apparently does not create hyperkalemia.[29] The distribution of urea in total body water, rather than solely in extracellular compartment, is the probable cause of the absence of hyperkalemia,[30] because there would be no fluid shifts from the intracellular into the extracellular compartment.

Metabolic acidosis also produces hyperkalemia by internal potassium shift.[31] Changes in the $CO_2$ content modulate the potassium level even when the extracellular pH does not change.[32] In this study, the serum $CO_2$ had a strong statistical correlation with the serum potassium, but hyperkalemia was not statistically different between episodes with and those without ketoacidosis. Furthermore, although the average decrease in the potassium per increase in arterial pH was consistent with published observations,[31] no statistical association between the change in the potassium concentration and that of the pH was found.

Neither hypertonicity[16] nor metabolic acidosis[3] is necessary for the development of hyperkalemia in patients with hyperglycemia. Insulin deficiency causes defective uptake of potassium by cells independently of any glucose or acid-base imbalance.[33] Insulin promotes potassium uptake by muscle cells in vitro even when the solution bathing the cells contains no glucose.[34] In patients receiving dialysis, insulin is the major mediator of cellular uptake of potassium infused intravenously.[35] We suggest that the correlations between the initial serum potassium and the other insulin-dependent initial variables, such as glucose, tonicity and $CO_2$ content, represent to some extent different manifestations of the same hormonal deficiency.[12,36] The combined biochemical effects, however, of lack of insulin accounted statistically for only .278 of the variability in the initial serum potassium level. Because insulin concentrations were not measured, a variation of insulin levels at presentation could account for an additional fraction of the variability in the initial potassium concentration. This fraction should be small because of the indirect evidence that initial insulin levels were low uniformly. Hyperglycemia[37] and the absence of insulin resistance in this study (administering low-dose insulin corrected the hyperglycemia in every instance) provide this indirect evidence. Therefore, factors other than insulin should be responsible for a great part of the variability in the initial serum potassium level. Potentially these factors include hormones, such as aldosterone and epinephrine,[33] uremia[4] and changes in external potassium balance. Several patients reported either protracted vomiting or consumption of large amounts of carbohydrates and potassium before admission, providing historical support for a role of external potassium balance in modulating a presenting serum potassium level.

Unlike influences on the initial potassium value, the effects of the infused insulin accounted statistically for the major part of the change in the potassium concentration during treatment. The statistical effect of the initial potassium level on the change in potassium was independent of the other variables and has clinical importance. Regardless of what factors determined the potassium concentration in the presence of hyperglycemia, insulin alone in amounts sufficient to correct the hyperglycemia restored the ability of internal potassium balance to regulate the serum potassium concentration. Thus, during treatment the decrease in the potassium value was great in patients presenting with hyperkalemia and small or none in patients presenting with normokalemia. After treatment, the potassium level was normal in most patients. Only two patients with normokalemia and ketoacidosis at presentation needed potassium replacement after treatment. Changes in serum potassium during treatment of hyperglycemia due to dialysis reported in two other studies agree with our findings. In five patients with no acid-base change during treatment, we found a significant correlation between the change in serum potassium and the initial potassium level.[3] We also calculated a significant correlation ($r = .884$, $P < .01$) between the change in potassium and the initial potassium concentration in the eight hyperglycemic episodes reported by Kaldany and colleagues.[24]

Diabetic patients receiving hemodialysis in whom hyperglycemia develops are at high risk of hyperkalemia whether or not they have associated acidosis. If there are associated catabolic states, patients on CAPD therapy in whom hyperglycemia develops are also at risk of hyperkalemia. In all hyperglycemic patients on long-term dialysis, the hypokalemic effect of the administered insulin is modulated by the initial serum potassium concentration, by the magnitude of the decrease in serum glucose and by correction of metabolic acidosis. Insulin is usually the only treatment needed for both hyperglycemia and hyperkalemia, but patients should be monitored both for signs of unstable hyperkalemia, which may dictate hypokalemic interventions faster than administration of insulin, and for the development of hypokalemia during treatment.

That insulin deficiency is a major determinant of hyperkalemia in hyperglycemia has been concluded from recent studies of different hyperglycemic states. In 142 episodes of ketoacidosis observed in 52 patients without advanced renal failure, Androgue and colleagues[38] studied the determinants of hyperkalemia by statistical methods similar to ours and concluded that insulin deficiency is the major cause of hyperkalemia. In a recent editorial,[39] the same conclusion was reached.

## REFERENCES

1. Legrain M, Rottembourg J, Bentchikou A, et al: Dialysis treatment of insulin dependent diabetic patients: Ten years experience. Clin Nephrol 1984; 21:72-81

2. Montoliu J, Revert L: Lethal hyperkalemia associated with severe hyperglycemia in diabetic patients with renal failure. Am J Kidney Dis 1985; 5:47-48

3. Tzamaloukas AH, Gardner KD Jr: Plasma potassium changes in anuric hyperglycemia treated with insulin. Am J Med Sci 1984; 287:27-30

4. Sterns RH, Cox M, Feig PU, et al: Internal potassium balance and the control of the plasma potassium concentration. Medicine (Baltimore) 1981; 60:339-354

5. McCurdy DK: Hyperosmolar hyperglycemic nonketotic diabetic coma. Med Clin North Am 1970; 54:683-699

6. Tzamaloukas AH, Levinstone AR, Gardner KD Jr: Hyperglycemia in advanced renal failure: Sodium and water metabolism. Nephron 1982; 31:40-44

7. Goldfarb S, Cox M, Singer I, et al: Acute hyperkalemia induced by hyperglycemia: Hormonal mechanisms. Ann Intern Med 1976; 84:426-432

8. Perez GO, Lespier L, Jacobi J, et al: Hyporeninemia and hypoaldosteronism in diabetes mellitus. Arch Intern Med 1977; 137:652-657

9. Perez GO, Lespier L, Knowles R, et al: Potassium homeostasis in chronic diabetes mellitus. Arch Intern Med 1977; 137:1018-1022

10. Rosenbaum R, Hoffsten PE, Cryer P, et al: Hyperkalemia after renal transplantation—Occurrence in a patient with insulin-dependent diabetes. Arch Intern Med 1978; 138:1270-1272

11. Popp D, Achtenberg JF, Cryer PE: Hyperkalemia and hyperglycemic increments in plasma potassium in diabetes mellitus. Arch Intern Med 1980; 140:1617-1621

12. Radó JP: A possible role for insulin in the prevention of glucose-induced paradoxical hyperkalemia during sodium depletion. Horm Metab Res 1980; 12:338-339

13. Nicolis GL, Kahn T, Sanchez A, et al: Glucose-induced hyperkalemia in diabetic subjects. Arch Intern Med 1981; 141:49-53

14. Rosestock J, Loizou S, Brajkovich I, et al: Effect of acute hyperglycemia on plasma potassium and aldosterone levels in type 2 (non-insulin-dependent) diabetes. Diabetologia 1982; 22:184-187

15. Ammon R, May W, Nightingale S: Glucose-induced hyperkalemia with normal aldosterone levels—Studies in a patient with diabetes mellitus. Ann Intern Med 1978; 89:349-351

16. McNair P, Madsbad S, Christiansen C, et al: Hyponatremia and hyperkalemia in relation to hyperglycemia in insulin-treated diabetic out-patients. Clin Chim Acta 1982; 120:243-250

17. Potter DJ: Death as a result of hyperglycemia without ketosis—A complication of hemodialysis. Ann Intern Med 1966; 64:399-401

18. Boyer J, Gill GN, Epstein FH: Hyperglycemia and hyperosmolality complicating peritoneal dialysis. Ann Intern Med 1967; 67:568-572

19. Whang R: Hyperglycemic nonketotic coma induced by peritoneal dialysis. J Lancet 1967; 87:453-456

20. Handa SP, Cushner GB: Hyperosmolar hyperglycemic nonketotic coma during peritoneal dialysis. South Med J 1968; 61:700-702

21. Gault MH, Ferguson EL, Sidhu JS, et al: Fluid and electrolyte complications of peritoneal dialysis—Choice of dialysis solutions. Ann Intern Med 1971; 75:253-262

22. Al-Kudsi R, Daugirdas J, Ing T, et al: Extreme hyperglycemia in dialysis patients. Clin Nephrol 1982; 17:228-231

23. Tzamaloukas AH, Avasthi PS: Temporal profile of serum potassium concentration in nondiabetic and diabetic outpatients on chronic dialysis. Am J Nephrol, in press

24. Kaldany A, Curt GA, Estes NM, et al: Reversible acute pulmonary edema due to uncontrolled hyperglycemia in diabetic individuals with renal failure. Diabetes Care 1982; 5:506-511

25. Moreno M, Murphy C, Goldsmith C: Increase in serum potassium resulting from the administration of hypertonic mannitol and other solutions. J Lab Clin Med 1969; 73:291-298

26. Makoff DL, Da Silva JA, Rosenbaum BJ: On the mechanism of hyperkalemia due to hyperosmotic expansion with saline or mannitol. Clin Sci 1971; 41:383-393

27. Viberti GC: Glucose-induced hyperkalaemia: A hazard for diabetics? Lancet 1978; 1:690-691

28. Tzamaloukas AH, Avasthi PS: Effect of hyperglycemia on serum sodium concentration and tonicity in outpatients on chronic dialysis. Am J Kidney Dis 1986; 7:477-482

29. Wolf A, McDowell MM: Apparent and osmotic volumes of distribution of sodium, chloride, sulfate and urea. Am J Physiol 1954; 176:207-212

30. Tzamaloukas AH, Jackson JE, Long DA: Hyperkalemia of hypertonic expansion in anuria—Differences from hyperosmolar expansion (Abstr). Physiologist 1986; 29:138

31. Androgue HJ, Madias NE: Changes in plasma potassium concentration during acid-base disturbances. Am J Med 1981; 71:456-467

32. Fraley DS, Adler S: Correction of hyperkalemia by bicarbonate despite constant blood pH. Kidney Int 1977; 12:354-360

33. Bia MJ, DeFronzo RA: Extrarenal potassium homeostasis. Am J Physiol 1981; 240:F257-F268

34. Zierler KL: Effect of insulin on potassium efflux from muscle in the presence and absence of glucose. Am J Physiol 1966; 198:1066-1070

35. Sterns RH, Feig PU, Pring M, et al: Disposition of intravenous potassium in anuric man: A kinetic analysis. Kidney Int 1979; 15:651-660

36. DeFronzo RA, Sherwin R, Felig P, et al: Nonuremic diabetic hyperkalemia—Possible role of insulin deficiency. Arch Intern Med 1979; 137:842-843

37. Foster DW: Insulin deficiency and hyperosmolar coma. Adv Intern Med 1974; 19:159-173

38. Androgue HJ, Lederer ED, Suki WN, et al: Determinants of plasma potassium levels in diabetic ketoacidosis. Medicine (Baltimore) 1986; 65:163-172

39. Hyperkalemia in diabetic ketoacidosis (Editorial). Lancet 1986; 2:845-846

# Use of Intravenous Pyelography in Blunt Trauma—A Reappraisal

JEROME R. HOFFMAN, MD; ROBERT R. SIMON, MD; MARC SMITH; GLENN STROM, *and* LARRY J. BARAFF, MD, *Los Angeles*

*The role of intravenous pyelography (IVP) in the evaluation of blunt abdominal trauma is controversial. Major renal injuries have occasionally been reported in the absence of hematuria, but the test is not always accurate, is expensive and has potential morbidity. By reviewing the charts of 150 consecutive patients seen in an emergency department who had IVP for blunt abdominal trauma, we evaluated the ability of clinical and laboratory findings to predict IVP findings, the incidence of abnormal findings on IVP and the number of times IVP affected patient management. Only one patient's management was found to be clearly affected by the results of the IVP. We feel, therefore, that IVP should be reserved in cases of blunt abdominal trauma for patients with gross hematuria and those with microscopic hematuria and suggestive clinical findings. The absence of hematuria should preclude the use of IVP unless there are other exceedingly strong clinical findings.*

(Hoffman JR, Simon RR, Smith M, et al: Use of intravenous pyelography in blunt trauma—A reappraisal. West J Med 1987 May; 146:576-579)

The diagnosis of urinary tract injury consequent to blunt trauma can be difficult, and the role of pyelography in which the dye is given intravenously (IVP) has been the subject of controversy. Some authors have proposed that IVP should be done in any patient with a suggestive injury, in light of the fact that significant renal or other urinary tract injury can occur in the absence of positive findings on urinalysis.[1-3] Others have noted the relative infrequency with which the results of IVP change the management of patients with blunt trauma and have suggested that it be reserved for patients with more specific indications.[4-6] Various clinical findings have been proposed as either necessary or sufficient indications for IVP following blunt trauma. These include any or all of the following: a suggestive mechanism of injury, back or flank pain, gross or microscopic hematuria, x-ray film findings of lower rib fractures, lumbar spine fractures or transverse process fractures in the upper lumbar spine.[7-9]

This study was designed to evaluate the usefulness of IVP in diagnosing urinary tract injuries in patients with blunt abdominal trauma and to determine whether any particular clinical or laboratory findings would correlate with the presence of abnormalities on IVP. We hypothesized that clinical and laboratory findings would not differentiate patients with abnormalities on IVP from those patients in whom posttraumatic IVP is normal. We also hypothesized that the results of IVP would rarely affect the clinical management of patients with blunt trauma because few renal or urinary tract injuries determined by IVP studies would require surgical or other specific intervention, and such injuries, when present, would be most likely to occur in the presence of associated injuries that would mandate a surgical procedure.

## Patients and Methods

We did a cohort study by reviewing the charts of 150 consecutive patients seen at the UCLA Emergency Medicine Center from April 29, 1981, to March 28, 1983, following blunt trauma for whom intravenous pyelography was done. No formal rules governing when to do an IVP were in force at the time the patients were seen. In general, an IVP was done following blunt trauma if there was any degree of hematuria, a suspicious mechanism of injury, clinical or x-ray film findings suggestive of upper urinary tract injury or if a patient required an abdominal operation for other reasons. There were also no strict criteria for doing a cystogram or a urethrogram. In general, cystography was done if an IVP showed a possible bladder injury, in patients with severe pelvic fractures and in patients with gross hematuria and pelvic pain. A urethrogram was usually done on patients with gross blood at the meatus, a free-floating prostate, severe pelvic fractures or in whom a Foley catheter could not be easily passed into the bladder.

By retrospective chart review we collected clinical information on each patient, including age, sex, mechanism of injury, presence or absence of suggestive signs and symptoms (including back pain, groin pain, abdominal tenderness and costovertebral angle tenderness), gross and microscopic hematuria, findings on plain x-ray films (transverse process, rib fractures or both), IVP results, performance of an associated abdominal procedure and hospital admission. Each element that could not be gathered by retrospective chart review was considered unknown and excluded from analysis. For example, we did not assume that back pain was absent if it was not specifically recorded on the chart. On the other hand,

From the Departments of Medicine (Dr Hoffman, Dr Simon, Mr Smith and Mr Strom) and Pediatrics (Dr Baraff), Division of Emergency Medicine, Center for the Health Sciences, UCLA School of Medicine, Los Angeles.

Reprint requests to Jerome R. Hoffman, MD, Department of Medicine, Division of Emergency Medicine, UCLA Center for the Health Sciences, 10833 LeConte Ave, Los Angeles, CA 90024.

objective findings, such as the presence or absence of transverse process fractures on x-ray study, which could be subsequently determined by x-ray film review, were always recorded as either positive or negative. We separated patients with urinary tract abnormalities on IVP from those whose IVP showed normal kidneys, ureters and bladder. IVPs that showed only pelvic hematoma were classified as normal. We compared a cohort of patients with abnormal IVP with the others to determine if any of the previously mentioned clinical or laboratory findings could distinguish between the two groups. Finally, we looked at each of the individual cases with an abnormal IVP to determine whether the IVP findings changed the clinical course of the patient and, if so, how.

*Statistical Methods*

Statistical analysis for nonparametric data was done by $\chi^2$ testing. Comparisons of continuous variables between the two groups were evaluated by analysis of variance. A $P$ value of .05 or less was considered statistically significant. Sensitivity, specificity and positive and negative predictive values were defined in the standard manner.

## Results

The patients' mean age was 28.4 ± 1.1 years, and 67% were male. The mechanism of injury of these patients is listed in Table 1. Most were involved in a motor vehicle accident (74%), either as the driver or passenger of an automobile or motorcycle or as a pedestrian; 16% were injured in falls.

Table 2 presents the clinical characteristics of these patients. When positive or negative documentation of their signs and symptoms was present in the medical record, the majority of patients had back pain, groin pain and abdominal tenderness. In all, 41% had costovertebral angle tenderness. Gross hematuria was present in 15% of patients. Transverse process fractures and lower rib fractures were present in 16% and 27%, respectively. All of these clinical signs and symptoms, except rib fractures, were more frequent in patients with abnormal IVP. Except for gross hematuria, however, these differences did not reach statistical significance, and in no case did the presence or absence of individual findings accurately predict IVP findings.

Table 3 presents a comparison between the amount of hematuria in the patients stratified by abnormal and normal IVP results. Of patients with abnormal IVP, 11% had fewer than 10 erythrocytes per high-power field, as opposed to 30% of patients with normal IVP. Of patients with abnormal IVP, 44% had gross hematuria as opposed to 14% of patients with normal IVP. All degrees of hematuria were more frequent in those patients with abnormal IVP; only the difference, however, in the rates of gross hematuria was statistically significant ($P = .02$). The sensitivity, specificity and positive and negative predictive values of gross hematuria for abnormalities as seen on IVP were 44%, 87%, 17% and 96%, respectively. The presence of microscopic hematuria of 10 or more erythrocytes per high-power field with regard to these same variables was 89%, 30%, 7% and 98%, respectively.

The clinical findings, IVP results and clinical course of the nine patients with multiple trauma and abnormal emergency department IVPs are presented in Table 4. Four patients were felt to have a renal contusion, two had extravasation of contrast material from the kidney and there was one instance each of unilaterally decreased excretion (felt to be possibly due to right renal vascular trauma), bladder rupture and displacement of the left kidney inferiorly by what was felt to be a large superior hematoma. All patients but one were managed without surgical treatment. One patient with possible extravasation was discharged from the emergency department after about 20 hours of observation. In two instances, renal injury was confirmed by other tests, one each by renal scan and renal angiogram. The patient whose IVP showed displacement of the left kidney possibly because of a large hematoma superiorly had a liver-spleen scan done that was interpreted as equivocal. That patient was taken to the operating room and had normal findings at laparotomy. All nine of these patients had at least one positive sign or symptom, gross hematuria or transverse process fracture.

Only patients whose intravenous pyelogram showed a defined injury to the kidneys, ureter or bladder were considered to have abnormal IVPs. In addition to the 9 patients with the

TABLE 1.—*Mechanism of Injury in 150 Patients With Multiple Trauma Who Had Intravenous Pyelogram in an Emergency Department*

| *Mechanism of Injury* | *Number (%)* |
|---|---|
| Automobile accident | 59 (39) |
| Auto *v* pedestrian | 27 (18) |
| Motorcycle accident | 26 (17) |
| Fall | 24 (16) |
| Assault | 6 ( 4) |
| Other | 8 ( 5) |

TABLE 2.—*Clinical Characteristics of 150 Patients With Multiple Trauma Who Had Intravenous Pyelogram (IVP) in an Emergency Department*

| *Clinical Characteristic* | *IVP Results (%)* | | *Total* | P |
|---|---|---|---|---|
| | *Abnormal* | *Normal* | | |
| Age, years* | 26.7±2.3 | 28.5±1.1 | 28.4±1.1 | NS |
| Sex, male | 4/9 ( 44) | 97/141 (69) | 101/150 (67) | NS |
| Back pain | 4/4 (100) | 70/88 (80) | 74/92 (80) | NS |
| Groin pain | 2/2 (100) | 24/81 (30) | 26/83 (60) | NS |
| Abdominal tenderness | 8/9 ( 89) | 74/131 (56) | 82/140 (59) | NS |
| CVA tenderness | 4/5 ( 80) | 18/49 (37) | 22/54 (41) | NS |
| Gross hematuria | 4/9 ( 44) | 19/141 (13) | 23/150 (15) | <.05 |
| Transverse process fracture | 3/9 ( 33) | 21/141 (15) | 24/150 (16) | NS |
| Lower rib fracture | 1/9 ( 11) | 40/141 (28) | 41/150 (27) | NS |
| Abnormal cystogram | 1/3 ( 33) | 1/27 ( 4) | 2/30 ( 7) | NS |

CVA=costovertebral angle, NS=not significant

*Mean ± standard error of the mean.

TABLE 3.—*Amount of Hematuria in 150 Patients With Multiple Trauma Who Had Intravenous Pyelogram (IVP) in an Emergency Department*

| *Hematuria (RBCs/hpf)** | *IVP Results* | | | |
|---|---|---|---|---|
| | *Normal, No. (%)* | *Abnormal, No. (%)* | *Total, No. (%)* | P |
| <10 | 42 (30) | 1 (11) | 43 (29) | >.05 |
| ≥10 | 99 (70) | 8 (89) | 107 (71) | >.05 |
| ≥20 | 83 (59) | 7 (78) | 90 (60) | >.05 |
| ≥30 | 72 (51) | 6 (67) | 78 (52) | >.05 |
| ≥50 | 62 (44) | 6 (67) | 68 (45) | >.05 |
| Gross hematuria | 19 (14) | 4 (44) | 23 (15) | =.02 |

*RBCs/hpf=erythrocytes per high-powered field.

noted abnormalities, 11 had IVPs that showed a pelvic hematoma. In none of these patients was any specific diagnostic test or therapy initiated as a result of this finding.

Of the 150 patients, 30 had a cystogram done. Two of these were abnormal, showing bladder rupture. In one of these patients, the IVP also showed bladder rupture. The other patient was a 35-year-old man with gross hematuria whose intravenous pyelogram was interpreted as normal. His bladder rupture was treated surgically, with no other indications for a surgical procedure. There were no abnormal urethrograms obtained on any of these patients.

## Discussion

It has been suggested that an IVP should be done almost routinely in patients with blunt trauma because of the occasional presence of significant renal injuries in patients who do not have any degree of microscopic or gross hematuria or significant clinical findings.[2,3] Most large series of patients receiving an IVP for multiple trauma, however, have failed to document the usefulness of this test.[4-6] An IVP is obtained on many patients with positive findings, and even when abnormalities are shown on IVP, rarely do these affect patient management.

McDonald and co-workers[4] showed that IVP results were not accurately predicted by clinical and laboratory findings (urinalysis) in 209 patients with blunt abdominal trauma. Of these patients, 18 had abnormal IVPs, and of these only 6 had gross hematuria, while the other 12 had microscopic hematuria. Only 9 of the 18, however, had abdominal exploration, and in 8 of these cases evaluation of associated injuries was the indication for a surgical procedure. Thus, IVP affected the management in only 1 of the 209 cases; other details of this patient's clinical and urinalysis findings are not separated out in the report.

Guice and colleagues[5] found that 13 of 156 patients (8%) had abnormal IVP after blunt trauma. Microscopic or gross hematuria was the indication for IVP. While 3 of 119 patients with microscopic hematuria had abnormal IVP, therapy was changed by IVP findings in none of them. All five patients who required further evaluation on the basis of IVP had gross hematuria, including the only patient of the 156 (0.6%) who required surgical therapy.

Levitt and associates reported 17 abnormal IVPs in 105 patients (16%) undergoing pyelography for blunt abdominal trauma.[6] Only 3 of these 17 required urologic surgical intervention, and all 3 had gross hematuria, suggestive clinical findings and at least one associated injury. In none of 83 patients without gross hematuria was the clinical course affected by IVP.

Sturm and Perry evaluated 92 patients with thoracic and lumbar transverse process fractures for the presence of associated injuries.[7] Urologic surgical injuries were absent in the 41 patients who did not have hematuria and were present in only 1 of 39 patients with microscopic hematuria. This was in contrast to the presence of such injuries in 4 of 12 patients with gross hematuria.

Griffen and co-workers, on the other hand, suggested that "all patients sustaining abdominal trauma should have an IVP regardless of whether of not hematuria is present."[2] This statement is based on the fact that in their review of 18 patients with presumed blunt renal trauma (as defined by one or more of abnormal IVP, presence of hematuria or operative findings), four did not have hematuria, two of whom underwent operative intervention. One of these two had a spleen removed, but no surgical procedure related to the genitourinary system; thus, only one patient with "renal trauma" without hematuria had clinical treatment changed by IVP. The authors do not clearly state how many patients had IVP during the time this one case was discovered, although they suggest there were 152 patients with "blunt abdominal trauma" seen at their institution during this period. Thus, even in this series from which the authors make an exceedingly strong statement about the value of IVP, the yield of this procedure seems to have been extremely low.

We reviewed 150 consecutive IVPs done at our institution in patients with blunt trauma because we suspected that the results of the IVPs usually did not change patient management. We attempted to find clinical markers that might help differentiate between patients with normal and abnormal IVPs so as to define reasonable criteria for doing IVPs following blunt trauma, and thus to limit the number of patients who need this test. While it is important to identify patients requiring specific care of major renal injuries, we noted that IVP is not only expensive (a total of $41,700 was spent on the 150 studies in our series) and time-consuming but carries significant risk (anaphylaxis, renal failure, delay to operation), and thus its costs might well outweigh its benefits if it only rarely contributes positively to patient management.

TABLE 4.—*Clinical Findings, IVP Results and Clinical Course in Nine Patients With Multiple Trauma and an Abnormal IVP in an Emergency Department (ED)*

| Patient | Age, yr | Sex | IVP Result | Back Pain | Groin Pain | Abdominal Tenderness | CVA Tenderness | Gross Hematuria | Transverse Process Fracture | Clinical Course |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 . . . | 18 | ♀ | Possible right renal vascular trauma | ? | ? | No | ? | No | Yes | Renal scan abnormal; conservative treatment |
| 2 . . . | 19 | ♂ | Left renal contusion | ? | ? | L | L | No | No | Conservative treatment |
| 3 . . . | 24 | ♂ | Extravasation, left lower pole | ? | ? | L | L | Yes | No | Conservative treatment; repeat IVP normal |
| 4 . . . | 25 | ♀ | Bladder rupture | ? | Yes | L | ? | Yes | Yes | Foley catheter |
| 5 . . . | 26 | ♀ | Possible right renal contusion | ? | ? | Yes | ? | No | No | Conservative treatment |
| 6 . . . | 28 | ♂ | Possible extravasation left kidney | Yes | Yes | R | No | No | No | Discharged from ED |
| 7 . . . | 29 | ♂ | Right renal contusion | Yes | ? | R | R | Yes | Yes | Conservative treatment |
| 8 . . . | 29 | ♀ | Right renal contusion | Yes | ? | R | R | Yes | No | Renal angiogram shows right lower pole laceration; conservative treatment |
| 9 . . . | 42 | ♀ | Displaced left kidney, large hematoma superiorly | Yes | ? | Yes | ? | No | Yes | Equivocal liver-spleen scan; normal findings on laparotomy |

CVA=costovertebral angle, IVP=intravenous pyelography, L=left, R=right, ?=questionable or equivocal

Our findings seem to show the lack of usefulness of IVP in most patients in whom it is done in the setting of blunt trauma. While there were no standard criteria for doing IVP during the time patients entered into this study were seen, IVP was generally done in patients for indications that are similar at many institutions, including the presence of microscopic or gross hematuria, a significant mechanism of injury, clinical findings such as groin or costovertebral angle (or both) pain and tenderness and significant plain x-ray film findings such as transverse process or lower rib fractures. Of 150 IVPs carried out for such indications, only 9 were abnormal. Of greater significance is the fact that of these 9 abnormal IVPs, none influenced therapy.

We had only limited success in differentiating patients with normal and abnormal IVPs. The best marker for separating these two groups was the presence or absence of gross hematuria, which was found in 4 of 9 (44%) patients with, as compared with 19 of 141 (44%) patients without, abnormal findings on IVPs ($P = .02$). The absence of gross hematuria, however, did not rule out an abnormal IVP (56% false-negatives), and its presence was not proof of abnormal IVP, since 19 of 141 (14%) patients with normal IVPs, including one with bladder rupture, had gross hematuria. Interestingly, one of nine patients with abnormal IVPs had fewer than 10 erythrocytes per high-power field on urinalysis, substantiating the belief that the absence of significant microscopic hematuria does not preclude an abnormal IVP. Nevertheless, 42 of 43 patients without even microscopic hematuria—fewer than 10 erythrocytes per high-power field—had normal IVP, suggesting that the absence of microscopic hematuria has an excellent negative predictive value for genitourinary tract injury as seen on IVP.

Besides gross hematuria, other clinical, laboratory and x-ray film findings are traditionally used in decision making regarding doing IVPs. While groin pain, abdominal tenderness and costovertebral angle tenderness were all more frequent in patients with abnormal IVP, these findings were only recorded as present or absent in a few of the patients in this series. It is impossible to meaningfully extrapolate from this small number to the entire group of patients in the series, as it is impossible in a study based on retrospective chart reviews such as this one to know whether or not these findings were positive in the much larger number of patients for whom they were not recorded.

In retrospect, it is apparent that IVP was not useful in many of the patients in our series. It could indeed be argued that it was virtually never useful and was misleading in the one patient who had abdominal surgical intervention for an intraperitoneal bladder rupture discovered by cystography. This is not to say that IVPs should never be done following blunt abdominal trauma. IVPs are important in patients undergoing exploratory laparotomy following trauma, to document the presence of two functioning kidneys if indeed surgical findings indicate the need for a nephrectomy on one side. IVPs are generally thought to be accurate in identifying renal lesions requiring surgical treatment, although they are clearly not always sensitive or specific in defining these lesions, as seen in the one patient in our series who did have an operation.

While there are no precise criteria to be gleaned from our study that would accurately identify all patients with abnormal IVP, or accurately exclude all patients with normal IVP, we suggest the use of significantly more stringent criteria in doing IVP following blunt abdominal trauma. We suggest that IVP should be done following blunt trauma in the presence of gross hematuria, or if there are 10 or more erythrocytes per high-power field on urinalysis in association with clinical findings suggestive of renal injury, including back pain, groin pain, transverse process fractures or a highly suggestive mechanism of injury such as a direct blow to the costovertebral area. Fewer than 10 erythrocytes per high-power field should exclude IVP except in the presence of very strong clinical indications. Additionally, IVP should be done in patients who will be undergoing exploratory laparotomy for other indications, so as to define the genitourinary tract anatomy and ensure the presence of two functioning kidneys. We think that the adoption of such criteria, which should thus be more stringent than those currently used at many institutions, would significantly decrease the number of IVPs done in this circumstance, while being highly unlikely to adversely affect the management of any patients.

#### REFERENCES

1. Bright TC, White K, Peters PC: Significance of hematuria after trauma. J Urol 1978; 120:455-456

2. Griffen WO Jr, Belin RP, Ernst CB, et al: Intravenous pyelography in abdominal trauma. J Trauma 1978; 18:387-392

3. Niemi T, Fisher RP, Gervin AS: Does microscopic hematuria affect major genitourinary injury in trauma? (Abstr). Ann Emerg Med 1983; 12:245

4. McDonald EJ, Korobkin M, Jacobs RP, et al: The role of emergency excretory urography in evaluation of blunt, abdominal trauma. AJR 1976; 126:739-742

5. Guice K, Oldham K, Eide B, et al: Hematuria after blunt trauma: When is pyelography useful? J Trauma 1983; 23:305-311

6. Levitt MA, Criss E, Kobernick M: Should emergency IVP be used more selectively in blunt renal trauma? Ann Emerg Med 1985; 14:959-965

7. Sturm JT, Perry JF Jr: Injuries associated with fractures of the transverse processes of the thoracic and lumbar vertebrae. J Trauma 1984; 24:597-599

8. Holcroft JW, Trunkey DD, Minagi H, et al: Renal trauma and retroperitoneal hematomas—Indications for exploration. J Trauma 1975; 15:1045-1052

9. Banowsky LH, Wolfel DA, Lackner LH: Considerations in diagnosis and management of renal trauma. J Trauma 1970; 10:587-597

# A Practical Approach to Improving Pain Control in Cancer Patients

MALCOLM L. BRIGDEN, MD, *and* JEFFREY B. BARNETT, BScPharm, *Victoria, BC*

*Despite a wealth of recent articles, many patients with cancer pain continue to suffer needlessly. The satisfactory treatment of cancer pain requires a variety of practical management strategies. Practicing physicians need a wider understanding of both the basic principles of analgesic therapy and the pharmacologic features of analgesics. Certain analgesics are best not used in cancer care. The use of pharmacologic adjuncts may lessen overall narcotic requirements and side effects. The appropriate use of alternative therapies can dramatically improve the quality of patients' overall survival.*

(Brigden ML, Barnett JB: A practical approach to improving pain control in cancer patients. West J Med 1987 May; 146:580-584)

Although many patients with cancer remain pain free in the early stages of their disease, about half eventually suffer pain.[1] In terminal cancer, pain is a problem in 75% of patients.[2] Experts estimate that despite a wealth of information on pain management, 25% of all cancer patients die without adequate pain control.[3]

## Illustrative Case

A 42-year-old woman with obstructive jaundice was found at an operation to have inoperable carcinoma of the pancreas, and palliative biliary decompression was done. Postoperatively the patient suffered severe pain in the anterior abdomen that radiated through to the back. While in hospital, the pain medication administered was meperidine hydrochloride (Demerol) to be given on an every-four-to-six-hour basis. Following discharge, an acetaminophen-codeine mixture was prescribed, but only on an "as-needed" basis. The patient, who was already concerned about addiction, was informed that constipation, mental changes and tolerance might all be associated with the regular use of pain medication. When the family reported persisting pain, they were told stronger drugs should be "kept in reserve" for the time that the patient was "terminally ill." For the next three months, the patient suffered episodic strong pain, especially when awaking during the night. In the last month of life, the patient was admitted to hospital with cachexia and a bedsore. Although still able to swallow, at this point the patient was given large doses of narcotics intramuscularly, resulting in drowsiness and confusion. Because the family believed the patient's disorientation was an unavoidable effect of medication, she remained isolated and uncommunicative for her last weeks.

This case shows many of the common errors in cancer pain management. With an understanding of the principles of analgesic therapy in patients with cancer, however, and the proper use of currently available analgesics, most such patients can have reasonable pain control without oversedation even in the last phases of illness.

## General Principles of Cancer Pain Management

Recent expert advisory committees on the management of severe chronic pain in patients with cancer have formulated realistic goals for cancer pain management (Table 1).[4,5] A first tenet is to establish an accurate etiologic diagnosis of any individual cancer patient's pain. Studies have shown that about 75% of cancer pain is associated with direct tumor involvement, while 20% will be related to cancer therapy, and the remaining 5% of patients may be suffering pain unrelated to cancer or its therapy.[3] Because cancer patients will often have many pains, a clear idea as to the cause of each individual pain is an essential step in control because different causes may suggest specific therapies. For example, pain due to direct tumor infiltration of bone will often respond well to palliative irradiation, whereas painful breast or prostate metastases may regress dramatically with appropriate hormone therapy. It is also important to remember that not all cancer pain is responsive to analgesic agents. Conventional analgesics may not help pains that are due to nervous tissue destruction, such as dysesthesia and causalgia, whereas steroids and the tricyclic antidepressants may be beneficial.[1]

There are several important general principles regarding the use of individual analgesic agents.[1,3,6] First, a sufficient dose of analgesic must be given to relieve pain. Patients who are denied an adequate dose of analgesic become preoccupied with pain and turn into "clock watchers," anticipating the arrival of the next medication dose. This fear and anxiety may actually augment analgesic requirements. Such patients may erroneously be seen by staff as demanding unreasonable amounts of narcotic and possibly displaying addictive behavior. Second, oral analgesics should be used for as long as possible because this allows the patient a mobile life-style. In addition, many terminally ill cachectic patients have less muscle mass, and parenteral injections can result in severe pain and limit mobility. Parenteral therapy should be used only when a patient cannot take medication via the oral or rectal route. Third, each dose of analgesic medication should be given on a prophylactic basis before the effects of the previous dose have worn off. The "as-needed" administration of analgesics not only results in suffering but can actually encourage the development of tolerance because pain is harder to control once it has recurred. Fourth, analgesic dosing must be tailored to each patient's needs and periodically reassessed and retitrated. For instance, increasing somnolence in a patient receiving a stable dose of narcotic may

From the Division of Medical Oncology, Victoria Cancer Clinic (Cancer Control Agency of British Columbia), Royal Jubilee Hospital, Victoria, British Columbia. Reprint requests to Malcolm L. Brigden, MD, Victoria Cancer Clinic, Royal Jubilee Hospital, 1900 Fort St, Victoria, BC V8R 1J8.

indicate that the dosage is now too high. This may be due to a reduced analgesic requirement, which often follows the initial control of severe pain, or may reflect a gradual decline in hepatic or renal elimination. Regular dosage reviews will also ensure that analgesics are adjusted appropriately if new side effects develop or pain worsens.

All strong analgesics have predictable side effects that should be anticipated.[1,3] Nausea, vomiting and constipation are probably the commonest side effects of narcotic therapy. Constipation is best treated prophylactically by keeping a patient well hydrated, active and on a regular regimen of stool softeners and laxatives. One such effective program consists of docusate sodium (dioctyl sodium sulfosuccinate [Colace]), 100 mg by mouth twice a day, combined with senna (Senokot S). Nausea and vomiting are often noted with the initial administration of narcotic analgesics due to stimulation of the chemoreceptor trigger zone in the medulla. An antihistamine such as dimenhydrinate (Gravol [Canada]; Dramamine, comparable US product), 50 mg every four hours, or a phenothiazine such as prochlorperazine (Stemetil [Canada]; Compazine, comparable US product), 5 to 10 mg every four hours, may be given a half hour before the narcotic. Antiemetics can often be withdrawn in the first few weeks of therapy because narcotic-associated nausea frequently decreases with time. Metoclopramide hydrochloride (Maxeran [Canada]; Reglan, comparable US product), 10 mg every four hours, may be especially useful when nausea is accompanied by dyspepsia. This antiemetic has the added benefit of not producing such phenothiazine side effects as sedation or a dry mouth. Respiratory depression is rarely a problem with narcotic therapy given orally because the plasma concentration of narcotic necessary to suppress respiratory drive seems to be higher than the concentration required for analgesia in most patients.[7] In addition, cancer pain itself is a major respiratory stimulus. Should respiratory depression inadvertently occur, however, naloxone hydrochloride (Narcan) is the narcotic antagonist of choice and may be given intravenously (IV), intramuscularly (IM) or subcutaneously.[1] The usual initial adult dose is 0.4 mg. If given in smaller doses of 0.1 to 0.2 mg IV at two- to three-minute intervals, it is often possible to restore respiratory function without counteracting the narcotic analgesic effect or precipitating withdrawal symptoms. Other narcotic side effects that may be seen are suppression of the cough reflex, bladder spasms and urinary retention.

There is no place for placebo therapy in cancer care.[1] About a third of patients with cancer may show a transient response to the administration of inert substances that they and their therapists believe will relieve pain. Endorphins may be involved in such placebo analgesic effects. Placebo responses do not indicate that a person's pain has a psychological basis or that the patient is exaggerating the reporting of pain. In fact, the use of placebos often provides no clinical information and results in patient anger and mistrust.

## Current Analgesics for Cancer Pain

With an understanding of the basic principles of analgesic therapy in cancer patients, a simple analgesic ladder may be constructed with only three levels (Figure 1).[8]

The first level consists of aspirin (acetylsalicylic acid) or aspirin-equivalent preparations. The analgesic effect of aspirin is often taken for granted due to its ready availability, but in double-blind trials, 600 mg of aspirin has been as effective as 60 mg of codeine for the relief of moderate cancer pain.[9] Both the therapeutic and toxic effects of aspirin are related to free drug concentration. Because there is extensive protein binding of aspirin, the free drug concentration is directly related to the serum albumin level. Cachectic patients with advanced cancer often have hypoalbuminemia and may require their aspirin dosage to be adjusted accordingly. Tinnitus is a common symptom heralding early aspirin toxicity. Patients should reduce their dosage when it is noted.

TABLE 1.—*Principles of Analgesic Therapy in Patients With Cancer*

| |
|---|
| Establish an etiologic diagnosis for each pain |
| Remember—not all cancer pain is responsive to analgesia |
| Use adequate analgesic doses |
| Use oral preparations whenever possible |
| Administer analgesics prophylactically to prevent pain—no PRN orders |
| Titrate analgesic doses individually for adequate control |
| Anticipate side effects—constipation, nausea |
| Never use placebos |

PRN=*pro re nata*, "as circumstances require"

| Progression | Agent | Alternatives |
|---|---|---|
| Nonnarcotic | ASA | Acetaminophen<br>Naproxen<br>Ibuprofen |
| ↓ | | |
| Weak narcotic | Codeine | Oxycodone HCl |
| ↓ | | |
| Strong narcotic | Morphine | Hydromorphone HCl<br>Levorphanol tartrate<br>Anileridine<br>Methadone HCl |

**Figure 1.**—The diagram shows the analgesic ladder for control of cancer pain. ASA = aspirin (acetysalicylic acid), HCl = hydrochloride

Acetaminophen is a reasonable substitute when the use of aspirin is contraindicated. On a milligram-for-milligram basis, acetaminophen is equivalent to aspirin in antipyretic and analgesic effects.[10] Acetaminophen, however, lacks the anti-inflammatory and antiprostaglandin effects of aspirin and should not be substituted if these are required.

Included as alternatives at the first level of the analgesic ladder are the wide variety of nonsteroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen (Motrin, for instance) and naproxen (Naprosyn). Like aspirin, these agents interfere with prostaglandin metabolism and may be beneficial in some cases of metastatic bone pain when osseous tumor deposits induce bone reabsorption by a prostaglandin mechanism. In general, despite pharmaceutical claims, all of the NSAIDs share aspirin's side effects, including gastric intolerance and the production to some degree of a qualitative platelet defect. Recent attention has also focused on the nephrotoxicity of these drugs, especially in older patients with compromised renal function.[11] Accordingly, these agents should be used cautiously in patients with kidney disease, ulcerative process, thrombocytopenia or any underlying qualitative platelet defect. Initial gastric intolerance may be reduced by taking the medication with food. For intractable heartburn, an alternative is the concomitant use of cimetidine (Tagamet), 300 mg by mouth three times a day, as required. Physicians should use the NSAID with which they have the most experience.

The second level of the analgesic ladder consists of weak narcotic agents of which codeine is an archetypal drug. The usual codeine dose for moderate pain is 30 to 60 mg.[9] While the dosing of morphine sulfate and other strong narcotics can

be increased almost indefinitely, nonnarcotics and weak narcotics tend to have a clinical "ceiling effect" after two to three dose increments where side effects increase proportionately more than analgesia.[8] With these medications, if pain control is not achieved within two or three adjustments, there is little point in further increases, and the patient should move up to the next rung of the analgesic ladder. Codeine is commonly included with aspirin or acetaminophen for additive effect. Popular combinations are aspirin with 30 mg of codeine or acetaminophen with 30 mg of codeine (such as Tylenol #3). The codeine equivalent oxycodone is a semisynthetic morphinelike narcotic agonist metabolized by similar pathways as codeine. Oxycodone hydrochloride is commonly prescribed in combination with aspirin (Percodan) or acetaminophen (Percocet).

The last rung of the analgesic ladder consists of morphine sulfate or equivalent agents. Because most patients with significant cancer pain will ultimately advance up the analgesic ladder, morphine has tended to be the "gold standard" against which other narcotic agents are compared.[1,3,8]

While a combination of morphine elixir, alcohol, cocaine and chloroform water (Brompton's cocktail) has been used in the past, recent practice is to use morphine solutions as single agents. Many patients objected to the bite of the alcohol in the combined preparation, and controlled trials showed cocaine added no analgesic effect, but could produce restlessness and hallucinations.[12] Commercial morphine solutions are available in a wide variety of concentrations including 1, 5, 10 and 20 mg per ml. For patients who prefer pills, morphine tablets are also available in various strengths including 5, 10 and 25 mg. In addition, a slow-release morphine tablet with prolonged duration of action (up to 12 hours) has recently been released in strengths of 30, 60 and 100 mg.[13]

When starting oral morphine therapy, the initial dose is usually 5 to 15 mg of solution. With oral morphine therapy, patients begin on an every-four-hour schedule and the next dose is given before the beneficial effect of the previous one has worn off. If pain is consistently relieved after individual doses but returns in less than four hours, the dose will have to be increased. Similarly, a dosage increment is obviously required when the initial starting dose does not consistently relieve pain. With oral morphine therapy, the usual increment is 50% of the first dose at the end of 24 to 48 hours when pain is not 90% controlled. If initial dosing controls pain but also results in significant somnolence, the next dose should be titrated downward by 25% to 50%. If titrating the dose upwards results in initial pain control that decreases with time, the dosing interval may be decreased. In practice, however, it is seldom necessary to use a shorter regimen than every four hours with administration of morphine orally. When first commencing therapy, if pain is not relieved after one or two analgesic increments of 50% to 100% or by decreasing the dose interval, consideration must be given to the possibility of narcotic-nonresponsive pain, as may be seen with degenerative nerve damage or bone destruction.

Careful assessment of total dosage every day or two during the first week of therapy is important. Once an adequate maintenance dose of oral morphine is established, individual patient requirements will often remain stable over long periods of time. Dosage escalation, however, may be required over a number of months, especially during the terminal phase of illness. Although Twycross found that more than 90% of patients with cancer would have their pain controlled with an oral morphine dose of 30 mg or less given every four hours, some individual patients with severe metastatic bone disease may require in excess of 2,000 mg a day.[4] While gradual increases in dose requirements with time may be due to the development of some degree of tolerance, sharp increases should always raise the possibility of progression of the malignant process.

TABLE 2.—*Checklist for Oral Morphine Sulfate Therapy*

| |
|---|
| Have I determined an appropriate starting dose? |
| Have I discussed drug side effects? |
| Have I discussed tolerance and dependence? |
| Have I prescribed an antiemetic? |
| Have I prescribed a laxative? |
| Have I explained dosage escalation if pain persists? |
| Has appropriate follow-up assessment been arranged? |

Initially it is very important to assess and deal with patients' prejudices regarding pain and the use of analgesics. Tolerance and dependence should be discussed in a realistic fashion.[4] Many patients have strong pharmacologic prejudices and fears that, commonly voiced, include "if I use the pain medication now, it won't work when I really need it," or "if I start taking these pills on a regular basis, I'll soon be hooked on them." Patients must be reassured regarding the fallacies of such beliefs. In addition, simply showing that the prophylactic use of analgesics conserves strength and energy will often ensure compliance and avoid "as needed" dosing. Table 2 is a checklist for oral morphine therapy.

Strong analgesics that may be used as morphine alternatives include hydromorphone hydrochloride (Dilaudid), levorphanol tartrate (Levo-Dromoran), anileridine (Leritine [Canada]) and methadone hydrochloride.[14] Hydromorphone is a morphine derivative that is much more soluble than the parent compound, although the half-life is slightly shorter (four hours).[14] This property has allowed the development of a high-potency form of the medication (Dilaudid-HP) that at 10 mg per ml is especially useful in cachectic patients requiring parenteral injections. It is our impression that the oral use of hydromorphone may possibly be associated with less nausea and constipation than morphine, although this has not been tested in clinical trials. This drug is our first choice in patients who have difficulty with oral morphine preparations. Levorphanol has a longer duration of action than morphine, often providing relief for as long as six hours (Table 3). Anileridine is similar in structure to meperidine, with a shorter half-life than morphine when given IM (two to four hours). Methadone is a synthetic molecule that has attracted considerable attention as a maintenance agent for heroin addicts. Methadone analgesia usually lasts from six to eight hours and there is no clear ceiling effect. When taken orally on a regular basis, methadone differs from morphine in several ways, including greater solubility with more predictable absorption and a longer half-life (more than 24 hours in many patients). When methadone therapy is first commenced, plasma concentrations often do not reach a steady state for four to five days, and cumulative effects with respiratory depression and hallucinations can occur. Great care must be taken when using this drug, especially in debilitated elderly patients or those with hepatic or renal dysfunction.[15]

Diamorphine (heroin) has recently been extensively publicized by the lay press and has been legalized for use in cancer patients in Canada.[16] Claims made on behalf of heroin versus

TABLE 3.—*Narcotic Comparison Chart*

| *Pharmacology and Pharmacokinetics* | *Morphine Sulfate* | *Codeine* | *Hydromorphone HCl* | *Levorphanol Tartrate* | *Anileridine* | *Methadone HCl* |
|---|---|---|---|---|---|---|
| Possible routes of administration . . | IM,PO,SC,IV | IM,PO,SC | IM,PO,SC,IV | IM,PO,SC,IV | IM,PO,SC | IM,PO,SC |
| Time to peak action, minutes . . . . | 15 | 15-30 | 15-30 | 15-30 | 15 | 30-60 |
| Duration of action, hours . . . . . | 4-5 | 4-6 | 4-5 | 4-5 | 2-3 | 3-5 |
| Half-life, hours . . . . . | 2-3.5 | 3 | 2-3 | 12-16 | . . . | 15-30 |
| IM equivalent dose, mg* . . . . . | 10 | 120 | 1.5 | 2 | 30 | 10 |
| Oral equivalent dose, mg* . . . . . | 20-30 | 200 | 7.5 | 4 | 50 | 20 |
| Oral:parenteral ratio . . . . . | High 1:2 | High 3:5 | Low 1:5 | Low 1:2 | High 3:5 | High 1:2 |

HCl=hydrochloride, IM=intramuscularly, IV=intravenously, PO=by mouth, SC=subcutaneously

*Equivalent to giving 10 mg morphine sulfate IM.

morphine include less nausea and constipation, increased mental alertness and greater solubility resulting in less painful intramuscular administration because a smaller injection volume can be used. Other than for increased solubility, these claims have not been substantiated in a number of well-conducted clinical trials. This is not surprising because pharmacologic studies have shown that in humans, heroin given orally is converted to morphine, actually providing only 80% of an equivalent oral dose.[17]

## Analgesic Agents to Be Avoided

Whereas no individual analgesic is absolutely contraindicated in patients with cancer, some drugs are best avoided. Propoxyphene napsylate (Darvon-N) has been noted in several controlled trials to be less effective than aspirin.[18] Adverse effects seen with therapeutic doses of this agent include nausea and vomiting and central nervous system (CNS) side effects such as dizziness and drowsiness. In our opinion, there is little indication for the use of this drug in patients with cancer. Pentazocine (Talwin) is a weak morphine antagonist that may precipitate analgesic withdrawal if given with other narcotic analgesics. In addition, this agent has a relatively short duration of action and may produce unpleasant side effects in many patients, including nausea, vomiting, blurred vision, drowsiness and hallucinations.[19] Because 10% of patients may experience such troublesome CNS side effects, the use of this analgesic is also best avoided in patients with cancer.

Meperidine hydrochloride (Demerol) is undoubtedly the analgesic most frequently misused in cancer patients.[1,3] Meperidine is a synthetic narcotic analgesic with atropinelike effects. Unfortunately, many physicians remain unaware of meperidine's short half-life of only two to three hours.[20] Because it is most frequently prescribed on an every-four-to-six-hour basis, inadequate pain control results. The short half-life along with poor absorption when given orally limit the use of meperidine for pain control in cancer patients. In addition, if oral doses of more than 200 mg every three hours are given, there is an increased incidence of toxic CNS effects including convulsions due to the accumulation of the metabolite normeperidine.[8]

## Parenteral Narcotic Therapy

Towards the end of many cancer patients' lives, parenteral administration of narcotic therapy becomes necessary. Morphine sulfate can be given parenterally by a variety of methods, including bolus injection (IV or IM), continuous drip (IV or subcutaneous) or by the epidural route. If a patient is in hospital, morphine may be given intravenously when oral therapy is no longer possible. Our protocol for a continuous morphine drip is provided in Table 4.

TABLE 4.—*Protocol for Morphine Sulfate Drip*

- Administer drug in a suitable intravenous (IV) solution and volume considering patients' 24-hour IV fluid requirements, such as 1,000 ml dextrose 5% in water
- Base the dose of morphine on previous 24-hour requirements; for instance, 20 mg given subcutaneously every 4 hours would convert to 120 mg per 24 hours at a rate of 5 mg per hour.
- Remember to reduce dose by 30% to 50% when converting from the oral or rectal routes
- Change the dose in 5-mg-per-hour increments as required and check blood pressure and respiratory rate regularly
- Do not add other ingredients to the infusion; they may be incompatible with morphine, and changes in infusion rate will result in changes in the administered dose of all ingredients

In some hospitals, the epidural administration of morphine is available and may offer some advantages, especially in those patients requiring such large morphine doses that a clouded sensorium results.[21] A number of possible complications have been noted with epidural therapy, including obstructed, broken or accidentally removed catheters and local infections including meningitis. In the future, the use of implantable delivery systems may overcome such problems. For the best analgesic results, it appears that an epidural catheter should be placed in relation to the dermatomes principally involved with the pain. Theoretically, delayed respiratory depression may be seen as long as 24 hours following each morphine dose. Intense pruritus and urinary retention have also been problems. For these reasons, this form of therapy is currently often reserved for those patients in whom conventional methods of analgesia have failed.

## Pharmacologic Adjuncts to Analgesic Therapy

Phenothiazines have long been used as analgesic adjuncts in combination with traditional narcotic therapy.[1,3] We use prochlorperazine in a dose of 5 to 10 mg given at bedtime to increase the effect of morphine. Initially, patients may be more sedated with such combination therapy, but using phenothiazines in this fashion often allows the reduction of total narcotic dose and lessens overall narcotic side effects. Phenothiazines are probably most useful when a combined sedative-antiemetic effect is desired. When purely anxiolytic or sedative effects are required, the benzodiazepines are preferable as they lack the autonomic side effects seen with phenothiazines. Physicians should use the benzodiazepine preparation with which they have the most clinical experience.

The tricyclic antidepressants have proved useful adjuncts in depressed patients. It has been noted that these agents in-

hibit the presynaptic reuptake of serotonin. This may explain their beneficial effect in neurogenically mediated pain because a variety of serotonin-dependent neuronal pathways are thought to exert inhibitory effects on pain transmission.[22] The tricyclic antidepressants have long half-lives and it is often unnecessary to give full therapeutic doses in patients who are also taking narcotics. Amitriptyline hydrochloride (such as Elavil), 25 to 75 mg taken at bedtime, will increase the chance of a good night's sleep, improve daytime mood and energy and may enhance analgesia.

The benefits of steroid therapy in terminally ill patients are frequently ignored.[1,3] Steroids are useful in those patients who have compressive or closed-space syndromes including brain or liver metastases, nerve or spinal cord compression and superior vena cava syndrome. Steroids are also helpful with painful boney metastases and tumor hypercalcemia. Patients with advanced carcinomatosis who have no medical contraindications to steroid therapy, such as peptic ulcer or hypertension, will often experience improved appetite, reduced incidence of fever and an enhanced sense of well-being when maintained on glucocorticoid therapy.[23] A typical regimen might consist of an initial prednisone dose of 1 to 2 mg per kg tapered over a period of two to three weeks to a maintenance dose of 10 to 15 mg a day.

## Other Therapeutic Measures

Nerve blocks are frequently underused in patients with cancer.[24] With metastatic involvement in the region supplied by the celiac plexus, as may occur with carcinoma of the stomach, pancreas or hypernephroma, celiac plexus block often results in gratifying palliation. This procedure can be done percutaneously on an outpatient basis. Patients are seldom left completely pain free, but the severity and biting nature of the pain is often reduced. Lumbar sympathetic blocks may be similarly effective with rectal, bladder or pelvic tumors involving the lumbosacral plexus that result in deep lancinating pain often referred to the anus. Cervical-thoracic sympathetic blocks may also be useful in some circumstances involving the upper extremities and neck. The benefits of individual blocks may not persist for more than a few months, but if initially successful, they can often be repeated.

There are a number of ablative neurosurgical procedures including various rhizotomies, percutaneous chordotomy and transsphenoidal hypophysectomy.[25] The discussion of these procedures is beyond the scope of this article. Because many of these operations result in significant life-long morbidity, they are usually used when conventional methods of pain control have proved unsatisfactory.

In addition, a wide variety of noninvasive adjunctive measures can be used in cancer pain control. These include such techniques as relaxation therapy, guided imagery, hypnotism, biofeedback, acupuncture and transcutaneous electric nerve stimulation.[26,27] For moderate pain, many of these modalities have been valuable adjuncts to drug therapy. Because none are uniformly suitable or available, such programs must be tailored to each patient's needs. At the very least, most physicians have access to audiocassettes that teach relaxation therapy using guided imagery.

## Postscript

Using the principles outlined in this article, our patient's history could be rewritten as follows:

A 42-year-old woman with obstructive jaundice was found at a surgical procedure to have an inoperable cancer of the pancreas, and palliative biliary decompression was done, along with a prophylactic celiac plexus block. Postoperatively, the use of analgesics was thoroughly discussed with the patient and family. The patient was discharged on a regimen of acetaminophen and codeine combined, to be taken regularly on an every-four-hour basis. The patient was also given an antiemetic and was started on a program of stool softeners and laxatives to prevent constipation. After a month's duration, when pain increased, the therapy was switched to oral morphine sulfate, again taken around-the-clock on an every-four-hour basis. The morphine dose was escalated as required over the next month to keep pace with any change in pain. After three months, the patient had a repeat celiac plexus block with good palliation, such that the total morphine dose could be reduced by 30%. In the last two weeks of life, she was admitted to hospital with increasing cachexia and a bedsore, unable to manage at home. At this time, the patient's therapy was switched to hydromorphone suppositories given on an around-the-clock basis, alternating with pills when tolerated. The patient died after three weeks in hospital, able to remain in communication with family and loved ones, and having experienced good pain control.

### REFERENCES


1. Tuttle CB: Drug management of pain in cancer patients. Can Med Assoc J 1985; 132:121-134

2. Cleeland CS: The impact of pain on the patient with cancer. Cancer 1984; 54:2635-2641

3. Foley KM: The treatment of cancer pain. N Engl J Med 1985; 313:84-95

4. Cancer Pain: Report of the Advisory Committee on the Management of Severe Chronic Pain in Cancer Patients. Ottawa, Health Protection Branch, 1984, Cat No. H42-2/4-1984

5. Health and Public Policy Committee, American College of Physicians: Drug therapy for severe, chronic pain in terminal illness. Ann Intern Med 1983; 99:870-873

6. Angell M: The quality of mercy (Editorial). N Engl J Med 1982; 306:98-99

7. Citron ML, Johnston-Early A, Fossieck BE Jr, et al: Safety and efficacy of continuous intravenous morphine for severe cancer pain. Am J Med 1984; 77:199-204

8. Twycross RG: Pain relief in cancer—Analgesics. Clin Oncol 1984; 3:91-107

9. Moertel CG, Ahmann DL, Taylor WF, et al: A comparative evaluation of marketed analgesic drugs. N Engl J Med 1972; 286:813-815

10. Jackson CH, MacDonald NC, Cornett JWD: Acetaminophen—A practical pharmacologic overview. Can Med Assoc J 1984; 131:25-32, 37

11. Linton AL: Adverse effects of NSAIDs on renal function (Editorial). Can Med Assoc J 1984; 131:189-191

12. Melzack R, Mount BM, Gordon JM: The Brompton mixture versus morphine solution given orally—Effects on pain. Can Med Assoc J 1979; 120:435-438

13. Moore RA, McQuay HJ, Bullingham RES, et al: Systemic availability of oral slow-release morphine in man. Ann Clin Biochem 1985; 22:226-231

14. Gourlay GK, Cousins MJ: Strong analgesics in severe pain. Drugs 1984; 28:79-91

15. Gourlay GK, Cherry DA, Cousins MJ: A comparative study of the efficacy and pharmacokinetics of oral methadone and morphine in the treatment of severe pain in patients with cancer. Pain 1986; 25:297-312

16. Barnett JB, Brigden ML: The great heroin myths. BC Med J 1985; 27:447-449

17. Inturrisi CE, Max MB, Foley KM, et al: The pharmacokinetics of heroin in patients with chronic pain. N Engl J Med 1984; 310:1213-1217

18. Miller RR, Feingold A, Paxinos J: Propoxyphene hydrochloride—A critical review. JAMA 1970; 213:996-1006

19. Forrest WH Jr: Oral pentazocine. Ann Intern Med 1974; 81:644-646

20. Reuler JB, Girard DE, Nardone DA: The chronic pain syndrome—Misconceptions and management. Ann Intern Med 1980; 93:588-596

21. Malone BT, Beye R, Walker J: Management of pain in the terminally ill by administration of epidural narcotics. Cancer 1985; 55:438-440

22. Fields HL, Levine JD: Pain—Mechanisms and management. West J Med 1984; 141:347-357

23. Bruera E, Roca E, Cedaro L, et al: Action of oral methylprednisolone in terminal cancer patients: A prospective randomized double-blind study. Cancer Treat Rep 1985; 69:751-754

24. Ferrer-Brechner T: Recent advances in managing cancer pain—The anesthesiologist's role. West J Med 1986; 144:597-598

25. Long DM: Relief of cancer pain by surgical and nerve blocking procedures. JAMA 1980; 244:2759-2761

26. Spiegel D: The use of hypnosis in controlling cancer pain. CA 1985; 35:221-231

27. Lack S: Pain relief in cancer—Non-invasive measures. Clin Oncol 1984; 3:167-179

# Hypoglycemic Syndrome in Infancy and Childhood

## A Surgeon's Perspective

A. R. MOOSSA, MD; LORI BAKER, MD, *and* M. LAVELLE-JONES, MD, *San Diego*

*Persistent, severe hypoglycemia due to inappropriate or excessive insulin secretion is an infrequent but devastating metabolic emergency in infancy and childhood. The primary therapeutic goal is to normalize blood glucose levels and to prevent the catastrophic sequelae of permanent brain damage and mental retardation due to refractory hypoglycemia. Overall, the use of diazoxide, the mainstay of medical treatment, has proved disappointing and has led to the reevaluation of aggressive, early surgical intervention. Currently, subtotal (80% to 90%) pancreatectomy is the most widely used operative procedure in the treatment of hyperinsulinism. It is, however, still associated with a relatively high failure rate, particularly in neonates or during early infancy when either nesidioblastosis or islet cell hyperplasia—both diffuse proliferative β-cell disorders—is the most common cause of inappropriate insulin secretion. In these cases, "total" or "near-total" pancreatectomy may be necessary to control the hypoglycemic crisis.*

(Moossa AR, Baker L, Lavelle-Jones M: Hypoglycemic syndrome in infancy and childhood—A surgeon's perspective. West J Med 1987 May; 146:585-588)

Transient, symptomatic hypoglycemia is the most common metabolic abnormality occurring in the first few days of life. Its incidence is 4 per 1,000 live-born term infants and 6 per 1,000 premature infants.[1] In most cases, neonatal hypoglycemia pursues a benign course[2] and will respond to relatively straightforward measures directed toward maintaining normal serum glucose levels. Persistent intractable hypoglycemia will supervene in less than 1% of these infants and, in contrast, is a medical emergency that calls for prompt recognition, thorough investigation and aggressive treatment if the devastating sequelae of permanent brain injury and mental retardation are to be avoided.

Inappropriate insulin secretion or "hyperinsulinism" accounts for as many as 50% of all cases of severe, unremitting hypoglycemia in infants younger than 1 year and is the second most common cause in children of all ages.[3]

### Pathogenesis of Hyperinsulinism

Insulin is the major hormone that regulates the storage of the products of intermediary metabolism. Specifically, insulin promotes peripheral glucose uptake in insulin-sensitive tissues such as skeletal muscle and adipose tissue and suppresses hepatic glucose production by inhibiting glycogenolysis and gluconeogenesis. In addition, insulin decreases the supply of fatty acid precursors for hepatic ketone body synthesis (a major energy source during starvation) by preventing adipose tissue lipolysis. In hypoglycemic syndromes due to hyperinsulinism, the combined effects of insulin hypersecretion on these pathways overwhelm the appropriate counterregulatory hormone responses and lead to a profound hypoglycemia. Thus, not only is the brain deprived of glucose as its primary source of energy during the most critical phase of its growth and development, but it is also deprived of all alternative energy sources.[3]

The demonstration of these specific actions of insulin excess on carbohydrate and fat metabolism, together with the lack of an appropriate metabolic response to profound hypoglycemia and starvation, is the principal means used to establish the diagnosis of hyperinsulinism.

### Pathologic Considerations

Various classifications[4,5] have been ascribed to the histologic appearances of the pancreas in hyperinsulinism. Essentially, the pathologic findings can range from a single functioning β-cell adenoma (insulinoma) to the diffuse disorders of islet cell hyperplasia and nesidioblastosis. Occasionally the pancreas may be histologically normal.[6] In general, diffuse lesions are more common in neonates and infants while adenomas predominate in later childhood.[7] Nesidioblastosis, a diffuse proliferation of the pancreatic β-cells, has only been described over the past 15 years as a distinct pathologic entity[8] and is currently the most frequent histologic diagnosis.[9] In this condition, new β-cells appear to arise from the pancreatic ductular epithelium and are believed to represent persistent fetal histologic elements.[10] Islet cell hyperplasia, in contrast, implies an increase in the number and size of normal islets. The pathologic distinction between islet cell hyperplasia and nesidioblastosis can be difficult to establish, as both conditions may coexist in the same gland[11]; furthermore, a combination of focal and diffuse lesions may be present.[12] Overall, the most severe pathologic lesions are usually seen in infants and neonates whereas the architectural changes are more subtle in older children.[13]

Attempts to correlate histologic appearances with functional disorders have been made using electron microscopy and immunofluorescent studies[13,14] and the predominance of β-cells in the aberrant islet cell tissue has been shown. The relative paucity of α (glucagon-secreting) and δ (somatosta-

From the Department of Surgery, University of California, San Diego, School of Medicine.
Reprint requests to A. R. Moossa, MD, Professor and Chairman, Department of Surgery, UCSD Medical Center, 225 Dickinson St, San Diego, CA 92103.

tin-secreting) cells shown on electron microscopic examination suggests that the inappropriate secretion of insulin may be caused, in part, by the disruption of the local paracrine secretory influences that regulate normal β-cell secretory function.[15]

## Clinical Features

The differential diagnosis of persistent hypoglycemia in infancy and childhood involves a large number of disorders. Moreover, in neonates many of the symptoms may be nonspecific. The onset, however, of a severe refractory hypoglycemia within a few hours of birth or the persistence of hypoglycemia beyond the first 2 weeks of life is highly suggestive of either an inborn error of metabolism or the existence of hyperinsulinemia.[9] Symptomatic hypoglycemia is a major clinical feature, especially in a neonate in whom evidence of central nervous system dysfunction predominates. During the first few months of life, hypotonia, jitteriness, lethargy, apnea and cyanosis, eye rolling, altered consciousness and major convulsions are common presenting manifestations of a low blood glucose concentration. Severe hypoglycemia is also a potent stimulus to catecholamine release, and the symptoms of sweating—pallor, tremor and tachycardia—may occur, particularly in later childhood.[7] Mental or psychomotor retardation and behavioral disorders may be present in older children in addition to convulsions; many will have had psychologic and intelligence testing before presentation.[16]

Physical examination is primarily of importance to detect hepatomegaly. Although in some infants with hyperinsulinism enlarged livers will develop during the first few days of life due to increased glycogen deposits, hepatomegaly, when present, usually implies a major metabolic defect in carbohydrate or amino acid metabolism.[16] In particular, glycogen-storage disease types I, III and VI, galactosemia, hereditary fructose intolerance and fructose 1,6-diphosphate deficiency need to be considered.[14] These can be excluded if blood pH, lactic acid and ammonia levels are normal and if the urine is free of ketones, amino acids and reducing substances.[14]

An additional clue to the clinical diagnosis of hyperinsulinism is the extremely limited tolerance to fasting seen in older infants and children. For most, a fast of three to six hours will precipitate a severe hypoglycemic attack.[17] In neonates, a suspicion should be raised if infusing a 10% to 15% dextrose solution fails to maintain normoglycemia, particularly when rates in excess of 8 to 10 mg per kg body weight per minute are required.[3]

In older children (18 months and older), ketotic hypoglycemia is the most frequent cause of persistent, severe hypoglycemic attacks and will require differentiation from a possible case of hyperinsulinism.[3] The specific pathogenesis of this condition is unknown, but a deficient release of gluconeogenic substrates, such as alanine, during stress or starvation may precipitate these hypoglycemic episodes.[18]

## Diagnosis

A rapid diagnosis is essential in patients with possible hyperinsulinism because further subclinical episodes of hypoglycemia can occur despite the vigorous measures used to maintain normoglycemia, thus compounding any preexisting brain injury.[9] Expeditious evaluation is important in an infant because the risk of further neurologic damage to a 10-day-old child is far greater than that in a 10-year-old child.[16]

It must be emphasized that a single laboratory determination rarely establishes the diagnosis of hyperinsulinism. Isolated serum insulin values are of little value, principally because the serum insulin levels are rarely elevated, particularly in a neonate.[16] Most authors would agree that a diagnosis of hyperinsulinism is likely if an inappropriately high insulin level exists during a hypoglycemic episode. The precise value remains of some debate. Pagliara and co-workers[19] consider a serum value greater than 10 μU per ml for a corresponding plasma glucose level of less than 40 mg per dl to be diagnostic, whereas others[13] consider the detection of any circulating insulin in the presence of hypoglycemia (plasma glucose level 40 mg per dl or less) to be highly significant.

The specificity of this concept of "relative" hyperinsulinemia can be enhanced by the simultaneous determination of β-hydroxybutyrate dehydrogenase, free fatty acid and serum growth hormone levels following the institution of a provocative fast.[3] In this diagnostic test, oral glucose administration or intravenous glucose supplementation is withdrawn and the decline in the plasma glucose level is closely monitored. When a level below 40 mg per dl is reached, a blood specimen is obtained to determine serum insulin, free fatty acid, β-hydroxybutyrate and growth hormone levels. At the conclusion of the phlebotomy, before recommencing glucose supplementation, an intramuscular injection of glucagon (1 mg) is administered to assess the hepatic response to glucagon under conditions of hypoglycemia.[20]

According to Stanley and Baker,[3] circulating fatty acid levels below 0.46 mmol per ml and β-hydroxybutyrate levels below 1.1 mmol per ml in the presence of serum insulin levels exceeding 12 μU per ml during hypoglycemia are diagnostic of hyperinsulinism. When serum insulin levels are less than 12 μU per ml, growth hormone studies will help exclude the diagnosis of panhypopituitarism, the other principal cause of suppressed ketogenesis during hypoglycemia.[3]

On a physiologic basis, low free fatty acid and β-hydroxybutyrate (the major circulating ketone body) levels indicate that lipolysis and ketogenesis are being aberrantly suppressed despite the stimulus of hypoglycemia. This finding is highly suggestive of inappropriate, excessive insulin secretion. The glycemic response to glucagon injection further aids the diagnosis of hyperinsulinism.[20] In normal persons, glycogen stores are mobilized during fasting to prevent hypoglycemia, and their depletion will limit the glycemic response to glucagon. A brisk response (a rise in the plasma glucose value of more than 30 mg per dl) to glucagon during hypoglycemia is indicative of inappropriate glycogen preservation caused by insulin-mediated inhibition of liver glycogenolysis.[20]

In children with ketotic hypoglycemia, a different response to controlled fasting and the glucagon challenge is observed and can be used to differentiate between the two conditions.[20] Typically, during symptomatic ketotic hypoglycemia, hepatic ketone body production and lipolysis are normal and are reflected by β-hydroxybutyrate levels greater than 2.75 mmol per ml and free fatty acid levels in excess of 1.55 mmol per ml.[3] In contrast to children with hyperinsulinemia, the response to glucagon is minimal because hepatic glycogen reserves have been mobilized during fasting.

Characteristically, plasma glucose levels in infants with hyperinsulinism are extremely labile, as attested to by the brief period of fasting necessary to provoke hypoglycemia. For this reason, provocative testing by administering leucine or tolbutamide, both potent insulin secretagogues, is no longer recommended as severe, refractory hypoglycemic attacks can be precipitated.[3,6]

## Medical Management

The management of an acute hypoglycemic episode depends on the prompt parenteral administration of glucose. Frazier recommends a bolus injection of 0.5 gram of glucose per kg body weight followed by a continuous infusion of 10% to 15% dextrose solution as required.[7] When these measures fail, or if a glucose requirement in excess of 10 mg per kg per minute persists, a trial of specific medical therapy is indicated. In the past, numerous agents have been used in an attempt to combat severe hypoglycemia. They include streptozocin, isoproterenol hydrochloride, adrenocorticotropic hormone, ephedrine, hydrocortisone and phenytoin. Most have met with relatively limited success or have been associated with unacceptable side effects. The use of diazoxide remains the current mainstay in the medical treatment of hyperinsulinism, although alternative regimens using somatostatin with or without glucagon are being evaluated.[4,21] Diazoxide, a nondiuretic benzothiazide, exerts its effect by directly suppressing insulin production from the pancreatic $\beta$-cells.[22] Current recommendations suggest that diazoxide be administered orally at a dose of 10 to 15 mg per kg per day in three to four divided doses up to a maximum dose of 20 mg per kg per day.[23] In most contemporary series, diazoxide is used as the first line of treatment in children of all ages with hyperinsulinism.[9,13,14,16,17,23,24]

Although initial reports on diazoxide were promising,[6,12,22] overall a response rate less than 50% has been achieved. The continued enthusiasm for its use reflects the observation that in some diazoxide-responsive children, permanent remission of hyperinsulinism can occur, thus obviating the need for surgical intervention.[3,23] For this reason, many authors continue to recommend a trial of diazoxide at a full dosage for 7 to 14 days.[9,16]

Of the several side effects associated with the long-term administration of diazoxide, hirsutism is the most frequent.[25] More serious, however, has been the onset of congestive cardiac failure[3] due to diazoxide-induced fluid retention and the occasional development of leukopenia and depressed circulating immunoglobin levels.[26]

## Surgical Treatment

Severe hypoglycemia that persists beyond the first two weeks of life and that is recurrent or unresponsive to diazoxide warrants prompt surgical exploration of the pancreas once alternative causes have been excluded. While most would agree on these indications for operative intervention, the optimal extent of pancreatic resection remains controversial.

As early as 1934, Graham and Hartmann reported on major pancreatic resection for intractable hypoglycemia,[27] and the standard procedure involving a 65% resection of the pancreas lateral to the superior mesenteric vessels was described by Gross in 1953.[28] The high incidence of recurrent hypoglycemia requiring either reoperation or continued medical therapy led Harken and colleagues and others to question the extent of resection and to advocate total extirpation of the pancreas, without duodenectomy, as the procedure of choice for hyperinsulinism.[29,30] Although Ravitch and Thomas have recommended a localized pancreatic excision if discrete pancreatic nodules are present,[31,9] most authorities have adopted a compromise approach of a variously defined 80% to 90% resection involving removal of all pancreatic tissue distal to the right side of the superior mesenteric vessels irrespective of the underlying pathology.[9,16,32] Schiller and associates recommend in addition resecting the medial third of the pancreatic head and the uncinate process.[14]

The issue of "total" or "near-total" pancreatectomy versus 80% to 90% subtotal pancreatectomy continues to be debated and reflects a continued dissatisfaction in the 25% to 50%[9,29] incidence of recurrent hypoglycemia following 80% to 90% subtotal pancreatectomy. The proponents of total pancreatic extirpation emphasize its greater ability to "cure" diffuse $\beta$-cell disease and thus minimize the risk of recurrent hypoglycemia.[29] Alternatively, there are those who consider this procedure to be excessive,[16] particularly if the underlying pathologic lesion is an adenoma, citing the high incidence of permanent endocrine and exocrine insufficiency[16] and the persistence of symptomatic hypoglycemia despite total pancreatectomy[24] as unacceptable sequelae. Recent reports, however, by Kramer and associates and Moazam and co-workers show the efficacy of "near-total" pancreatectomy as the procedure of choice in infants and neonates—that is, those age groups in whom severe hypoglycemia is most frequently caused by nesidioblastosis.[13,24] Both reports cite the inadequacy of initial subtotal pancreatectomy, with satisfactory glycemic control only being achieved by a subsequent near-total pancreatic resection. Furthermore, these authors suggest that long-term pancreatic exocrine and endocrine insufficiency following total or near-total pancreatectomy are not inevitable and that their resolution may be an index of the regenerative ability of those cell nests of pancreatic tissue that are inevitably retained following any attempt to totally remove the pancreas without duodenectomy. Thus, by definition, "total" pancreatectomy with duodenal preservation is effectively only near total in extent.

Unfortunately, there are few indices either before or during an operation to aid a surgeon in determining the extent of resection. Retrospective analysis supports the notion that, overall, adenomatous lesions are successfully treated by surgical excision more frequently than diffuse hyperplasia or nesidioblastosis.[3,29] In particular, infantile adenomata that are rarely responsive to medical therapy can often be effectively treated by partial pancreatectomy.[32] Conversely, lesser resections are often of least benefit to those children with nesidioblastosis.[13] These observations are, however, of limited value in the prospective evaluation of a patient as there are rarely any clues to the underlying pathologic process.

Preoperatively, the clinical presentation, serum glucose and insulin levels and the response to diazoxide are of no predictive value as to the cause of hyperinsulinism. Noninvasive imaging methods such as computed tomography or ultrasonography also have no place in the evaluation of these cases, as the small size of any focal pathologic lesion (less than 5 mm) is well below the normal limit of resolution of these techniques.[3] Similarly, selective angiography and pancreatic vein sampling techniques are of no value in the localization or diagnosis of the underlying disease process.[33]

At operation, the pancreas invariably appears normal on inspection and palpation, and only rarely can a solitary adenoma be identified. Frozen section examination is also noncontributory. The existence of an adenoma is frequently only revealed by the meticulous examination of serial sections, and special histochemical methods are required for the documentation of nesidioblastosis.[8] These techniques are necessarily time-consuming and cannot be applied to frozen section histologic analysis at the time of operation. During the resection,

alteration in plasma glucose concentration forms no reliable guide to the adequacy of resection.

Thus, a surgeon doing pancreatic resection for hyperinsulinism must frequently be guided solely by his or her philosophy and experience with regard to the extent of resection. Our current approach is to carry out a "90%" pancreatectomy, removing the distal pancreas, uncinate process and most of the pancreatic head, leaving about a third of the pancreatic head attached to the duodenal loop. We reserve near-total pancreatectomy for those in whom severe symptoms of hypoglycemia persist following an operation[33] despite additional diazoxide therapy.

Because hyperinsulinism is an uncommon clinical entity, the world's experience in the management of this condition is predominantly based on anecdotal retrospective surgical reports. To this, the authors add their 13-year total experience with this disorder comprising five infants treated by 90% subtotal pancreatectomy. One required reoperation for further pancreatic resection to control refractory hypoglycemia.

### *The Operative Procedure*

Laparotomy is carried out through a transverse supraumbilical abdominal incision. The lesser sac is exposed widely to allow complete visualization and exploration of the entire pancreas. With few exceptions, the pancreas appears normal to inspection and palpation. Resection commences distally, and the pancreas is carefully mobilized from the spleen. Preservation of the spleen is essential, using either the splenic vascular pedicle or short gastric vessels because late postsplenectomy sepsis, especially pneumoccal septicemia, is common in this age group.[34] About 90% of the pancreatic tissue is removed, including the uncinate process and distal two thirds of the pancreatic head. The pancreatic duct, if identified, is oversewn, the pancreatic bed drained and the abdomen closed using nonabsorbable sutures.

After the operation, the plasma glucose concentration is closely monitored. Transient hyperglycemia that is exquisitely sensitive to insulin is not infrequent and requires correction. Should hypoglycemia persist and be refractory to further medical therapy, we advocate early reoperation, within 48 hours, to achieve as near a total pancreatectomy as possible with duodenal preservation. Under these circumstances, the pancreatic remnant is resected through the original transverse incision, taking care to ligate the pancreaticoduodenal tributaries outside the duodenal wall to preserve the integrity of the pancreaticoduodenal arterial arcade and to prevent ischemic damage to the duodenum and distal common bile duct. The duodenum is thus left in situ with islands of pancreatic tissue on its concavity. Insulin and oral pancreatic exocrine supplements are given as required postoperatively.

## Conclusion

Pancreatectomy is a safe procedure that is well tolerated in infants and children and is associated with a low mortality rate irrespective of the extent of resection in this age group. The therapeutic goal in the treatment of hypoglycemia due to hyperinsulinism is to prevent brain damage. Historically, the high incidence of mental retardation was the sequel to prolonged and recurrent hypoglycemia, and the prognosis was especially bleak in infants with early-onset hypoglycemia when the abnormality was not promptly corrected. Currently, the behavioral disorders and convulsions that persist despite the control of hypoglycemia are probably still an indication of permanent damage induced by protracted evaluation and delayed operative intervention.[9]

The relative merits of near-total pancreatectomy in the management of hyperinsulinism will become clearer as further experience is accrued with this procedure and the overall incidence of postoperative endocrine or exocrine insufficiency becomes apparent. The ability of this procedure to relieve hypoglycemia or to improve subsequent control of previously intractable symptoms may render near-total pancreatectomy the procedure of choice in the future in all cases of hyperinsulinism.

### REFERENCES


1. Behrman RE, Vaughan VC: Hypoglycemia, chap 17.6, Nelson Textbook of Pediatrics. Philadelphia, WB Saunders, 1983, pp 1421-1431
2. Varma SK: Hypoglycemia in infancy and childhood. South Med J 1979; 72:57-64
3. Stanley CA, Baker L: Hyperinsulinism in infants and children: Diagnosis and therapy, *In* Barness LA (Ed): Adv Pediatr 1976; 23:315-355
4. Hirsch HJ, Loo S, Evans N, et al: Hypoglycemia of infancy and nesidioblastosis—Studies with somatostatin. N Engl J Med 1977; 296:1323-1326
5. Galdabini JJ, McNeeley BV: Case 30-1978—Case records of the Massachusetts General Hospital: Weekly clinicopathological exercises. N Engl J Med 1978; 299:241-248
6. Baker L, Kaye R, Root AW, et al: Diazoxide treatment of idiopathic hypoglycemia in infancy. J Pediatr 1967; 71:494-505
7. Frazier SD: Hypoglycemia, chap 9, Pediatric Endocrinology. New York, Grune & Stratton, 1980, pp 277-309
8. Yakovac WC, Baker L, Hummeler K: Beta cell nesidioblastosis in idiopathic hypoglycemia of infancy. J Pediatr 1971; 79:226-231
9. Thomas CG Jr, Underwood LE, Carney CN, et al: Neonatal and infantile hypoglycemia due to insulin excess: New aspects of diagnosis and surgical management. Ann Surg 1977; 185:505-517
10. Shermeta DW, Mendelsohn G, Haller JA Jr: Hyperinsulinemic hypoglycemia of the neonate associated with persistent fetal histology and function of the pancreas. Ann Surg 1980; 191:182-186
11. Misugi K, Misugi N, Sotos J, et al: The pancreatic islet of infants with severe hypoglycemia. Arch Pathol Lab Med 1970; 89:208-220
12. Jaffe R, Hashida Y, Yunis EJ: Pancreatic pathology in hyperinsulinemic hypoglycemia of infancy. Lab Invest 1980; 42:356-365
13. Kramer JL, Bell MJ, DeSchryver K, et al: Clinical and histologic indications for extensive pancreatic resection in nesidioblastosis. Am J Surg 1982; 143:116-119
14. Schiller M, Krausz M, Meyer S, et al: Neonatal hyperinsulinism—Surgical and pathologic considerations. J Pediatr Surg 1980; 15:16-20
15. Unger RH, Dobbs RE, Orci L: Insulin, glucagon and somatostatin secretion in the regulation of metabolism. Annu Rev Physiol 1978; 40:307-343
16. Campbell JR, Rivers SP, Harrison MW, et al: Treatment of hypoglycemia in infants and children—Surgical considerations. Am J Surg 1983; 146:21-28
17. Gauderer M, Stanley CA, Baker L, et al: Pancreatic adenomas in infants and children: Current surgical management. J Pediatr Surg 1978; 13:591-596
18. Pagliara AS, Karl IE, De Vivo DC, et al: Hypoalaninemia: A concomitant of ketotic hypoglycemia. J Clin Invest 1972; 51:1440-1449
19. Pagliara AS, Karl IE, Haymond M, et al: Hypoglycemia in infancy and childhood—Part II. J Pediatr 1973; 82:558-577
20. Finegold DN, Stanley CA, Baker L: Glycemic response to glucagon during fasting hypoglycemia: An aid in the diagnosis of hyperinsulinism. J Pediatr 1980; 96:257-259
21. Bougnères PF, Landier F, Garnier P, et al: Treatment of insulin excess by continuous subcutaneous infusion of somatostatin and glucagon in an infant. J Pediatr 1985; 106:792-794
22. Mereu TR, Kassoff A, Goodman AD: Diazoxide in the treatment of infantile hypoglycemia. N Engl J Med 1966; 275:1455-1459
23. Landau M, Perlman M, Meyers SM, et al: Persistent neonatal hypoglycemia due to hyperinsulinism: Medical aspects. Pediatrics 1982; 70:440-446
24. Moazam F, Rodgers BM, Talbert JL, et al: Near-total pancreatectomy in persistent infantile hypoglycemia. Arch Surg 1982; 117:1151-1154
25. Koblenzer PJ, Baker L: Hypertrichosis lanuginosa associated with diazoxide therapy in prepubertal children: A clinicopathological study. Ann NY Acad Sci 1968; 150:373-382
26. Combs JT, Grunt JW, Brandt IK: Hematologic reactions to diazoxide. Pediatrics 1967; 40:90-92
27. Graham EA, Hartmann AF: Subtotal resection of the pancreas for hypoglycemia. Surg Gynecol Obstet 1934; 59:474-479
28. Gross RE: The Surgery of Infancy and Childhood. Philadelphia, WB Saunders, 1953, p 574
29. Harken AH, Filler RM, AvRuskin TW, et al: The role of "total" pancreatectomy in the treatment of unremitting hypoglycemia of infancy. J Pediatr Surg 1971; 6:284-289
30. McFarland JO, Gillett S, Swemer RJ: Total pancreatectomy for hyperinsulinism in infants. Surgery 1965; 57:313-318
31. Ravitch MM: The pancreas in infants and children. Surg Clin North Am 1975; 55:377-385
32. Rich RM, Dehner LP, Okinaga K, et al: Surgical management of islet-cell adenoma in infancy. Surgery 1978; 84:519-525
33. Moossa AR, Dhorajiwala JM: Surgery of the endocrine pancreas, chap 19, *In* Moossa AR: Tumors of the Pancreas, 1st Ed. Baltimore, Williams & Wilkins, 1980, pp 505-520
34. Eraklis AJ, Filler RM: Splenectomy in childhood: A review of 1,413 cases. J Pediatr Surg 1972; 7:382-388

# Clinicopathologic Conference

## Multiple Cerebral Emboli in a Young Man

MARK P. NESPECA, MD, *and* JEANNETTE J. TOWNSEND, MD, *Salt Lake City*

JEANNETTE J. TOWNSEND, MD: The patient, a 28-year-old man, had had generalized seizures for several years. He was apparently well until a week before his admission at the University of Utah Medical Center (UUMC). At that time the patient was admitted to a local hospital because of fever and dehydration due to vomiting and diarrhea. Evaluation revealed no abnormalities of the throat, a negative stool culture and normal chest x-ray film. During this week of hospital stay, he continued to have fevers, diarrhea, malaise and arthralgias. On the night before transfer, the patient was found to have acute aphasia with a right hemiparesis. A serum phenytoin concentration was 2.3 μg per ml and the phenobarbital level was 16 μg per ml. The clinical diagnosis was postictal paralysis, and phenytoin was intravenously administered. The patient was then transported to UUMC for further evaluation.

His medical history indicated that he was born prematurely with a birth weight of 2,041 grams (4 lb 8 oz). He was noted to be cyanotic in the neonatal period but was discharged home on the fifth postnatal day. He was a "slow learner" in school. His seizure disorder was fairly well controlled on a regimen of phenobarbital, phenytoin and carbamazepine. He had had hepatitis as a child with complete recovery. At age 17 he was treated for a bleeding peptic ulcer that resolved. At age 23 he was treated for hypertension. He had smoked two packs of cigarettes per day for the past ten years. He had a history of homosexuality. A test for the human immunodeficiency virus antibody one month before admission was negative. There was no history of head trauma, alcoholic intake or operations. There were no known allergies and no family history of thromboembolic disease, seizures or arthritis. Admission to UUMC a month before this admission for evaluation of his chronic seizures did not document any fevers, intestinal problems or arthralgias.

On arrival the patient was dysphasic and awake but not moving his right side. He was able to follow some simple commands with his left hand. Vital signs showed a temperature of 38.3°C (101.8°F), pulse 76 and regular, respirations 28, blood pressure 120/76 mm of mercury. He was tall and mildly obese, weighing 109 kg (240 lb). Head, eyes, ears, nose and throat examination showed a supple neck, mild pharyngeal erythema without exudate or adenopathy, normal ocular fundi and no evidence of trauma. There was no rash or adenopathy. Chest auscultation revealed diminished breath sounds in all fields and bibasilar rales. On cardiovascular examination there was no jugular venous distension but there were normal first and second heart sounds except for a question of a split $S_1$. There was no murmur, gallop or rub. There were no carotid bruits and both carotids had normal palpable pulses. His liver edge was palpable 3 cm below the right costal margin. The spleen was not enlarged and there were no abdominal masses or areas of tenderness. Results of a rectal examination were normal, including a negative test for occult blood in the stool. Genitalia were normal.

On neurologic examination he had a nonfluent severe dysphasia. When asked to show two fingers to the examiner, his best response consisted of lifting up his left arm. There was conjugate eye deviation to the left. Pupils were 5 mm, equal and reactive to light. There was pronounced right lower facial muscle weakness. Corneal reflexes were intact though slower on the right. Gag response was diminished but present. Motor examination revealed a substantial right hemiparesis and normal power in the left arm, hand and leg. He appeared to respond to pinprick stimuli in both arms and legs with purposeful withdrawal on his left side. Deep tendon reflexes were 1/4 and symmetric in the upper extremities and 2/4 and symmetric in the lower extremities. Plantar responses were present and flexor bilaterally.

Laboratory studies on admission elicited the following values: serum sodium 138 mEq per liter, potassium 3.7 mEq per liter and glucose 104 mg per dl; alkaline phosphatase 146, lactic dehydrogenase 172, aspartate aminotransferase 33, alanine aminotransferase 56 and γ-glutamyltransferase 203 IU per liter; urate 5.6, calcium 8.6 and phosphorus 2.8 mg per dl; total protein 5.6 and albumin 3.1 grams per dl; cholesterol 147 and total bilirubin 0.5 mg per dl, and magnesium 2.0 mEq per liter. A complete blood count showed the following: leukocyte count 6,300 per μl with 73% polymorphonuclear neutrophils, 3% bands, 17% lymphocytes, 3% monocytes and 4% eosinophils; hemoglobin 14.9 grams per dl; hematocrit 44%; normal indices, and platelets 229,000 per μl. Prothrombin time was 15.3 seconds with control 12.3 seconds. Partial thromboplastin time was 34 seconds with control 37 seconds. Westergren sedimentation rate was 5 mm per hour. A rapid plasma reagin test was nonreactive. The antinuclear antibody test was negative at less than 1:20. A drug screen revealed a phenobarbital concentration of 16 μg per ml, a carbamazepine concentration of 1.2 μg per ml and a phenytoin concentration of 7.0 μg per ml. Analysis of a urine specimen obtained after placement of an indwelling catheter showed a specific gravity of 1.029, pH 5, trace protein, trace glucose, moderate blood, no ketones, bilirubin or nitrites.

(Nespeca MP, Townsend JJ: Multiple cerebral emboli in a young man—University of Utah [Clinicopathologic Conference]. West J Med 1987 May; 146:589-595)

From the Departments of Neurology (Drs Nespeca and Townsend) and Pathology (Dr Townsend), University of Utah School of Medicine, Salt Lake City.
Reprint requests to Jeannette J. Townsend, MD, Associate Professor, Department of Pathology, University of Utah School of Medicine, Salt Lake City, UT 84132.

ABBREVIATIONS USED IN TEXT

CSF = cerebrospinal fluid
CT = computed tomography
2-D = two-dimensional
ECG = electrocardiogram
$P_{CO_2}$ = partial pressure of carbon dioxide
$P_{O_2}$ = partial pressure of oxygen
UUMC = University of Utah Medical Center

The microscopic examination showed 20 to 50 erythrocytes per high-power field and 10 to 20 leukocytes per high-power field, no bacteria, casts or crystals and 3+ mucus. Arterial blood gas determinations done while the patient was receiving 6 liters per minute of oxygen showed pH 7.49, partial oxygen pressure ($P_{O_2}$) 112 torr, partial carbon dioxide pressure ($P_{CO_2}$) 35 torr and $O_2$ saturation at 94%.

A nonenhanced computed tomographic (CT) scan of the brain revealed a low-density lesion involving most of the left middle cerebral artery distribution without areas of hemorrhage (Figure 1). There was obliteration of the left sylvian fissure. A portable x-ray film of the chest showed a questionable left lower lobe infiltrate, but no other abnormalities. An electrocardiogram (ECG) showed sinus bradycardia with 58 beats per minute, a PR interval of 0.12 seconds, QRS 0.08 seconds, QT 0.52 seconds and axis 0°. There were large T waves in leads II and $V_2$ through $V_4$.

The cerebrospinal fluid (CSF) examination showed an opening pressure of 240 mm water with 1 leukocyte and 1 erythrocyte per $\mu$l and no xanthochromia. The protein level was 36 mg per dl and the glucose 69 mg per dl. A Gram's stain and bacterial culture were negative.

The patient was treated with oxygen by nasal cannula, intravenous administration of phenytoin and phenobarbital and carbamazepine given per nasogastric tube. A regimen of high-dose dexamethasone was begun in an attempt to minimize brain swelling. On the second hospital day, cerebral angiography revealed occlusion of the left internal carotid artery with a narrowing beginning 1 cm distal to its origin and gradually tapering over several centimeters to complete occlusion at about the level of C1-2 (Figure 2). There was no evidence for collateral flow from the external carotid to intracerebral vessels. The right internal carotid and right vertebral arteries were normal. Both anterior cerebral arteries were perfused by the right internal carotid. No cross filling to the left middle cerebral artery was seen.

The angiogram was felt to be most consistent with a carotid dissection. Heparin therapy was begun with an intravenous bolus followed by continuous infusion. A CT scan taken before initiation of this therapy again showed no hemorrhage but continued mass effect with obliteration of the sylvian fissure. There was no known history of recent head or neck trauma or of chiropractic manipulation.

Because of the possibility of pneumonia on admission, the patient was given clindamycin parenterally. Fevers abated within 48 hours, and he remained afebrile until the seventh hospital day when a fever of 38.8°C (101.8°F) developed. Repeat chest x-ray film showed resolution of the infiltrate and no new infiltrates. Blood cultures were negative. Culture of a urine specimen from an indwelling catheter grew $10^5$ colonies per ml each of *Klebsiella, Escherichia coli* and *Proteus*. He was given gentamicin sulfate intravenously, but continued to have intermittent diarrhea. The clindamycin therapy was discontinued. Stool culture, examination for ova and parasites and a *Clostridium difficile* toxin assay were all negative.

Heparin resistance was noted. After numerous heparin boluses and increasing infusion rates, the patient finally had a

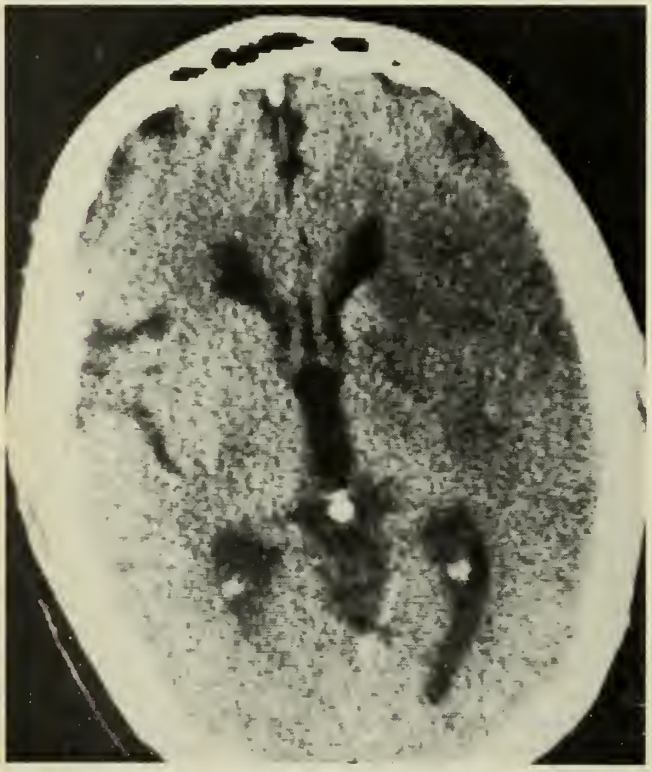


**Figure 1.**—An unenhanced computed tomographic scan shows a nonhemorrhagic low-density lesion on the left.

**Figure 2.**—An angiogram shows tapered occlusion of the left internal carotid artery.

partial thromboplastin time of 78 seconds with a control of 36 seconds on the 12th hospital day while receiving a heparin infusion at a rate of 2,500 units per hour.

The patient was obtunded on the second and third hospital days. He awoke on the fourth hospital day and remained conscious for the next ten days. There was no improvement in his language comprehension or production. Reflexes remained present on the right, but no motor responses could be elicited on that side. His left gaze preference diminished.

On the 13th hospital day, the patient was found cyanotic with bilateral upper extremity clonic activity followed by tonic rigidity of all extremities. Arterial blood gas determinations made after the event showed $Po_2$ 57 torr, $Pco_2$ 32 torr and pH 7.47 with the patient breathing room air. Electrolytes, glucose, calcium and magnesium levels were normal. Serum drug concentrations showed phenytoin 7.3 $\mu$g per ml, phenobarbital 24 and carbamazepine 3.5 mg per ml. His temperature was 38.8°C and a chest x-ray film showed new infiltrates at both bases. The patient did not regain consciousness. He had intermittent decerebrate posturing on the left side with decorticate posturing on the right. Pupils were 5 mm and reactive to light. Corneal and oculovestibular reflexes were present. Decerebrate posturing on the left was present with ipsilateral noxious stimuli. Bilateral extensor plantar responses were noted.

The patient was placed on a ventilator for respiratory support though spontaneous breathing persisted. A repeat CT scan done at this time showed no hemorrhage. A repeat study two days later revealed new low-density foci in the left occipital and basal ganglia region and in the region of the right basal ganglia (Figure 3).

Heparin therapy was discontinued and dexamethasone therapy resumed. A trial of mannitol produced no neurologic improvement. An echocardiogram showed normal left ventricular chamber size, wall thickness and motion. The other cardiac chambers and great vessels were normal. No abnormalities of any cardiac valves were found. Doppler recordings showed no regurgitation. No source for emboli was found. Two days after the heparin therapy was discontinued, protein C, protein S and antithrombin III levels were measured, with no evidence of deficiency found.

The patient's condition was unchanged on the 19th hospital day. Ventilatory support was withdrawn, and he died on the 20th hospital day.

## Discussion

MARK P. NESPECA, MD: The annual reported incidence for stroke in persons younger than 35 years in the United States has varied from 0 to 8 per 100,000.[1] Strokes in the young provide diagnostic and therapeutic dilemmas, as shown by the case reported herein. In this age group, nonhemorrhagic stroke is usually associated with a predisposing systemic disease affecting the heart or the extracranial or intracranial vascular system. Table 1 provides a list of systemic diseases to consider in a young person with an ischemic cerebral infarction. A few disease states are manifested only by cerebrovascular pathologic lesions (Table 2).

His history and findings on physical examination exclude several possibilities such as cyanotic congenital heart disease, a cardiac operation, sickle cell anemia, hypertension, diabetes mellitus, nephrotic syndrome, phakomatoses, homocystinuria (95% have dislocated lens), steroid therapy, fat embolism and mastoiditis. Laboratory studies either eliminate or reduce the likelihood of his stroke being related to leukemia, thrombocytosis, polycythemia, coagulation factor deficiencies, hypercoagulable state, cardiac dysrhythmia, nephrotic syndrome or meningitis. Cerebrospinal fluid findings provided strong evidence against neurovascular syphilis, which in recent years may be the most common form of neurosyphilis.[2] It is always hard to be certain that illicit drugs are not part of the clinical spectrum. The history and physical examination findings did not suggest this, and the fact that he was in his local hospital for a week before his stroke should have reduced access to such agents.

Severe dysphasia prevented the patient from giving an extensive history, and thus little was known about various aspects of his recent illness, except that fever, diarrhea and arthralgias of recent onset were present. He had not had these symptoms one month before admission when he was evaluated for chronic seizures. Had these intestinal complaints been more chronic, one could implicate inflammatory bowel disease predisposing him to stroke.[3] His tall stature, mild obesity and lack of occult blood in the stool argue against his having Crohn's disease or chronic ulcerative colitis. Acute gastroenteritis with dehydration is associated with cerebral venous or dural sinus thrombosis and could have caused the patient's symptoms. The CT scan, however, documented arterial occlusion as opposed to venous occlusion, and the unenhanced CT scan did not show the zones of patchy increased density within zones of low attenuation, cerebral hemorrhage or gyral enhancement commonly associated with cortical venous thrombosis.[4]

The CT evidence of arterial disease leads us to consider the disorders listed in Table 2. A recent study found athero-

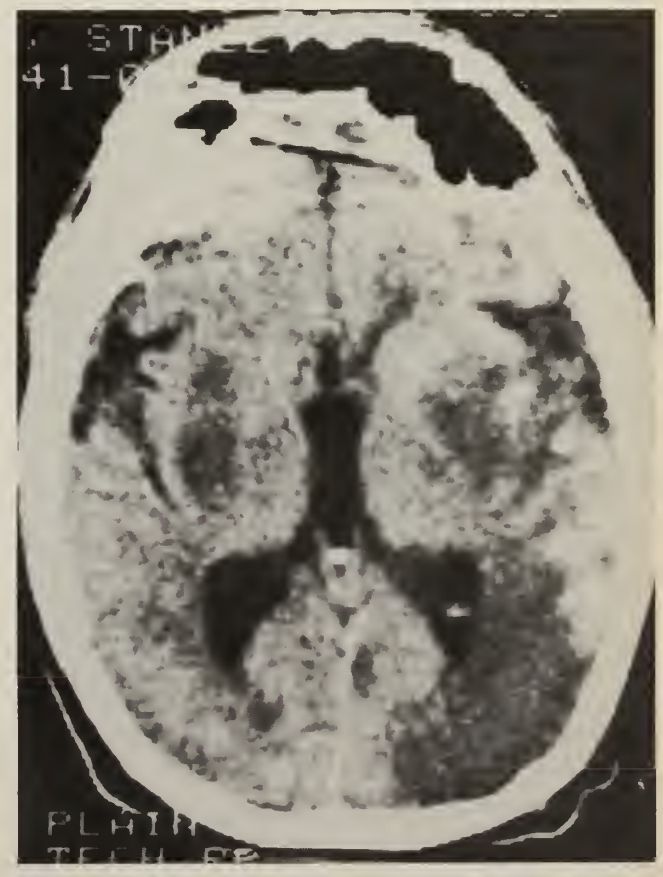


**Figure 3.**—A final computed tomographic scan shows new low-density lesions bilaterally.

sclerosis to be the cause of nonhemorrhagic cerebral infarction in 27% of 144 patients aged 15 to 45 years.[5] All but three of these had definable risk factors such as cigarette smoking, hypertension, diabetes mellitus or hyperlipidemia. This patient did have a history of cigarette smoking and transient hypertension, but there was no evidence of any atherosclerotic changes in the right carotid or cerebral circulation to suggest that this was the cause of his stroke.

Traumatic causes of nonhemorrhagic stroke were unlikely, although recent neck trauma could not be ruled out. There was no evidence on examination of intraoral injury, and cervical spine trauma would be more likely to compromise the posterior cerebral circulation. The patient clearly had anterior circulation ischemia as seen with carotid dissection, which can occur either with or without trauma.

Granulomatous angiitis is an uncommon disease that can occur at any age and has no particular sex or age predilection. Symptoms usually consist of a subacute encephalopathy with headache, nausea, vomiting and alteration of mental state. A fourth of patients have fever, chills and weight loss and in most, focal signs such as hemiparesis, dysphasia, seizures or visual loss ultimately develop. Unlike our patient, however, 80% of patients have an elevated CSF protein level and 90% have a CSF pleocytosis ranging as high as 180 cells per $\mu$l with a lymphocytic predominance.[6] Angiography shows segmental narrowing and irregularity of small distal vessels. Only 50% of patients show angiographic abnormalities. Large vessels may be involved but this is uncommon. Slightly more than half of the patients have a mild to moderate elevation in the sedimentation rate. Associations with Hodgkin's disease, *Mycoplasma* and herpes zoster have been reported but arthralgias and diarrhea are not seen.[7]

Cranial arteritis (giant cell arteritis) can be eliminated from consideration primarily by virtue of the patient's age and the normal sedimentation rate. Takayasu's arteritis (pulseless disease) involves the aorta and vessels that arise from its arch. This is a disease of unknown cause and has been reported primarily in women of Asian extraction. It is usually preceded by constitutional symptoms of fever, weight loss and night sweats and also has an associated elevation of the sedimentation rate.

Fibromuscular dysplasia of the internal carotid artery is another uncommon cause of stroke. This is more common in middle-aged women. The vessel can undergo spontaneous dissection, aneurysmal formation or thromboembolic events leading to cerebral infarction. Diagnosis is made by angiography, which can show alternating zones of widening and narrowing of the artery (string of beads), unifocal or multifocal tubular stenosis or aneurysmal dilatation of the affected vessel.

Cerebral angiography in this patient revealed a tapered occlusion of the left internal carotid artery that spared the carotid bulb. This finding is most typical of carotid dissection.[8-10] Although fibromuscular dysplasia is often associated with dissection, there were no angiographic features suggestive of fibromuscular dysplasia in the contralateral carotid system. In addition, the results of the angiogram did not suggest granulomatous angiitis or Takayasu's arteritis.

Dissections of the extracranial carotid artery are most common in the middle adult years, with a peak incidence at age 45. They may occur at any age and have no definable gender predilection. This condition often appears spontaneously in otherwise healthy persons, but may be associated with underlying arteriopathy or various types of trauma. Cystic medial degeneration was often reported in early autopsy studies but examination of surgical specimens has shown dissections occurring in arteries that are either microscopically normal or show only disorganized, fragmented elastic fibers.[11] Other arteriopathies associated with dissection include fibromuscular dysplasia, Marfan's syndrome, atherosclerosis, syphilitic arteritis and hypertension. Hyper-

TABLE 1.—*Systemic Conditions Predisposing to Ischemic Stroke in Young Patients*

| |
|---|
| Cardiac Disease |
| Cyanotic congenital heart disease |
| Rheumatic heart disease |
| Dysrhythmias |
| Infective endocarditis |
| Other valvular disorders, such as mitral valve prolapse |
| Atrial myxoma |
| Cardiac operation |
| Myocarditis |
| Infection |
| Meningovascular syphilis |
| Bacterial or fungal meningitis |
| Viral encephalitis or meningitis |
| Gastroenteritis with dehydration |
| Mastoiditis |
| Hematologic and Neoplastic Diseases |
| Sickle cell anemia |
| Leukemia |
| Coagulation factor abnormalities, such as antithrombin III, protein C or protein S deficiency |
| Thrombocytosis |
| Metastatic neoplasms |
| Polycythemia |
| Trauma |
| Intraoral trauma to carotid artery |
| Fat embolization with long bone fracture |
| Carotid dissection |
| Cervical spine trauma with vertebral artery trauma |
| Miscellaneous |
| Systemic lupus erythematosus |
| Periarteritis nodosa |
| Hypertension |
| Diabetes mellitus |
| Nephrotic syndrome |
| Inflammatory bowel disease |
| Phakomatoses—neurofibromatosis, Sturge-Weber syndrome, tuberous sclerosis |
| Homocystinuria |
| Steroid therapy |
| Oral contraceptives |
| Illicit drugs—amphetamines, phencyclidine, LSD, "lookalikes," heroin |
| Local mass effect of skull-based tumor, retropharyngeal abscess or brain tumor |

TABLE 2.—*Primary Disease of the Cerebral Vasculature*

| |
|---|
| Fibromuscular dysplasia |
| Carotid dissection, nontraumatic |
| Takayasu's arteritis |
| Cranial (temporal) arteritis |
| Granulomatous angiitis |
| Moyamoya disease |
| Atherosclerosis |

extension and rotational injury to the neck along with blunt trauma and penetrating wounds have all been associated with dissection. It is interesting to note that dissection can occur after trivial trauma such as coughing, blowing the nose or brushing the teeth or with common sports such as tennis, volleyball or bowling. Presentation with an initial massive stroke, however, is uncommon with dissection, probably occurring in no more than 5% of cases. Recurrent transient ischemic attacks are more common after dissection. Most patients have associated severe headache or neck pain, and many will have pulsatile tinnitus or an ipsilateral Horner's syndrome. Transient monocular blindness is also commonly reported.

Most authors recommend anticoagulant therapy in patients with carotid dissection to minimize the likelihood of secondary thrombotic or embolic infarction. Heparin therapy was begun in this patient, and his hospital course was marked by intermittent fevers and diarrhea, heparin resistance and resolution of the infiltrates on the chest radiograph. When adequately anticoagulated, however, he had acute neurologic deterioration due to new cerebral infarctions in the right and left basal ganglia and left occipital lobe. The bilateral lesions virtually eliminated carotid dissection as the source of his cerebral disease.

We are thus left with the task of explaining multiple nonhemorrhagic infarctions occurring in small and large vessels in both the middle and posterior cerebral circulations. Arthralgias and gastrointestinal symptoms commonly occur along with fever and rash in patients with polyarteritis nodosa, but signs and symptoms of peripheral neuropathy are much more common (60% to 70% have neuropathies) than cerebral infarction (less than 10%) and tend to precede the latter.[6] The other possible vasculitides have already been discussed.

Bilateral lesions without evidence of vasculitis suggest embolic events and compel us to take a closer look at the heart in this young man. Advances in cardiac, cerebral and vascular imaging have shown that about 25% of strokes are caused by heart lesions. In patients younger than 45 years, cardiac pathology may be responsible for as many as 50% of nonhemorrhagic strokes.[12] In this patient, results of the admission evaluation did not point toward cardiac pathology, as the cardiac examination showed no abnormalities. There was a normal cardiac silhouette on chest film, and an ECG showed only mild sinus bradycardia. No dysrhythmias or hypotension was noted in his first few days in an intensive care unit with frequent monitoring. It was only after the appearance of subsequent infarction that a two-dimensional (2-D) echocardiogram was done. No evidence of mitral valve prolapse or atrial myxoma was found. The most common angiographic abnormality in young patients with mitral valve prolapse and cerebral ischemic symptoms is branch occlusion, followed by middle cerebral artery occlusion and then internal carotid artery occlusion.[12,13] Our patient did not have evidence of branch occlusion but rather a tapered occlusion of the internal carotid. A tapered occlusion that spares the carotid bulb, although common in carotid dissection, could conceivably be mimicked by embolic or thrombotic disease.[8,9]

Acute viral myocarditis is often associated with fever and may be associated with other systemic symptoms. Signs of congestive heart failure or dysrhythmias or both are usually present, especially if cardiac dysfunction is severe enough to provide a locus for the formation of mural thrombi. A normal echocardiogram showing no abnormalities in wall motion provides compelling evidence against a severe viral myocarditis, but does not exclude a milder form of involvement.

The arthralgias and fever suggest the diagnosis of acute rheumatic fever with associated carditis. It is hard to explain his diarrhea on this basis, but the persistence of the diarrhea may have been due to the continuous antibiotic therapy after his admission. Beyond a history of arthralgias and evidence of fever, we have little else to support a diagnosis of acute rheumatic fever. There was no previous history of rheumatic heart disease or recent scarlet fever. On physical examination he had no evidence of polyarthritis, cardiac murmur, chorea, erythema marginatum or subcutaneous nodules. His throat culture was negative at the referring hospital. The sedimentation rate was normal and the PR interval was not prolonged. The normal echocardiogram argues against active rheumatic carditis.

Finally, we must consider infective endocarditis as the cause of this clinical spectrum.[14,15] This would still not explain his diarrhea. He had no known history or evidence of congenital or acquired cardiac disease predisposing him to endocarditis. Neither did the patient have an elevated sedimentation rate, anemia, abnormal urinary sediment or peripheral signs of embolization outside the central nervous system. He did have microscopic hematuria that could have been due to renal infarcts.

Fever, arthralgias and multiple cerebral emboli in a young patient, however, force us to consider endocarditis despite the above considerations. The patient had at least three sets of blood cultures done, with at least one set before antibiotic therapy. The use of clindamycin and gentamicin may have inhibited bacterial growth in subsequent cultures, and 15% of patients with bacterial endocarditis may have a negative first blood culture.

A normal 2-D echocardiogram does not exclude endocarditis. About 20% to 50% of patients with infective endocarditis may fail to show vegetations. The minimum detectable size of vegetations is usually 2 mm, and this increases with

**Figure 4.**—The low-power micrograph shows adherent thrombus in the left ventricle. The myocardium can be seen at the bottom of the picture (hematoxylin-eosin, × 65).

increasing distance beyond 7 cm from the transducer.[16] Limitations of the echocardiogram in defining other cardiac sources of emboli have been shown by various studies.[17] The sensitivity for detecting mural thrombi after myocardial infarction varies from 72% to 95%. In one study the smallest detected thrombus was 2.0 by 2.0 by 1.5 mm.[18] We are thus unable to exclude a cardiac source of emboli on the basis of a normal 2-D echocardiogram.

It is clear from the foregoing discussion that this clinical state of fever, arthralgias, diarrhea and multiple nonhemorrhagic cerebral infarctions with no abnormalities found on a cardiac examination and normal sedimentation rate, ECG and 2-D echocardiogram is difficult to reconcile with the disorders discussed above. Multiple cerebral infarctions, however, compel us to implicate primary cardiac disease, and the most likely cardiac disease causing multiple emboli in a young man with a normal echocardiogram would be infective endocarditis. This would explain his fever and arthralgias. Secondary consideration would be given to acute rheumatic fever without the usual associated features and viral myocarditis, either of which could cause associated mural thrombi undetected by echocardiography.

## Pathology

DR TOWNSEND: The autopsy was limited to examining the heart, liver, the bifurcation of the internal and external carotid artery on the left and the brain. Sections were taken but the organs were returned to the body.

The heart weighed 580 grams. The external surface was normal and there were no abnormalities of the valves. An adherent thrombus measuring 1.5 by 0.8 by 0.3 cm was found at the apex of the left ventricle (Figure 4). The myocardium grossly appeared normal. The other chambers were free of thrombus and the right ventricle showed mild hypertrophy.

At the bifurcation of the left internal and external carotid artery, the internal carotid artery was distended with a firm clot. This clot extended to involve both the left anterior and left middle cerebral arteries within the cranial vault.

The brain weighed 1,700 grams. The surface of the left hemisphere was softened and discolored, and the gyri were flattened. There was no evidence of uncal herniation, but moderate atrophy was present in the frontal lobes. The brain was cut in the fresh state, and the area of softening on the left involved the basal ganglia and the frontal, parietal, temporal and occipital lobes in the distribution of the left anterior, middle and posterior cerebral arteries. A discolored softened area was also found in the right putamen measuring 2 by 3 cm. The ventricles were enlarged. The cerebellum and brain stem showed no abnormalities.

Sections of the heart showed a diffuse myocarditis with perivascular chronic inflammatory cells and areas of fibrinous necrosis between muscle bundles. These areas were nodular in appearance and contained Anitschkow's myocytes (Figures 5 and 6). The inflammatory infiltrate associated with these interstitial nodules included lymphocytes, histiocytes, occasional plasma cells, eosinophils and polymorphonuclear leukocytes. These cellular Aschoff bodies represent the classic proliferative stage seen in the heart of patients who have acute rheumatic fever with carditis. The apical thrombus showed beginning organization and adherence to the endocardium. The thrombus was composed of platelets, fibrin and occasional mononuclear cells. No organisms were found on special stains.

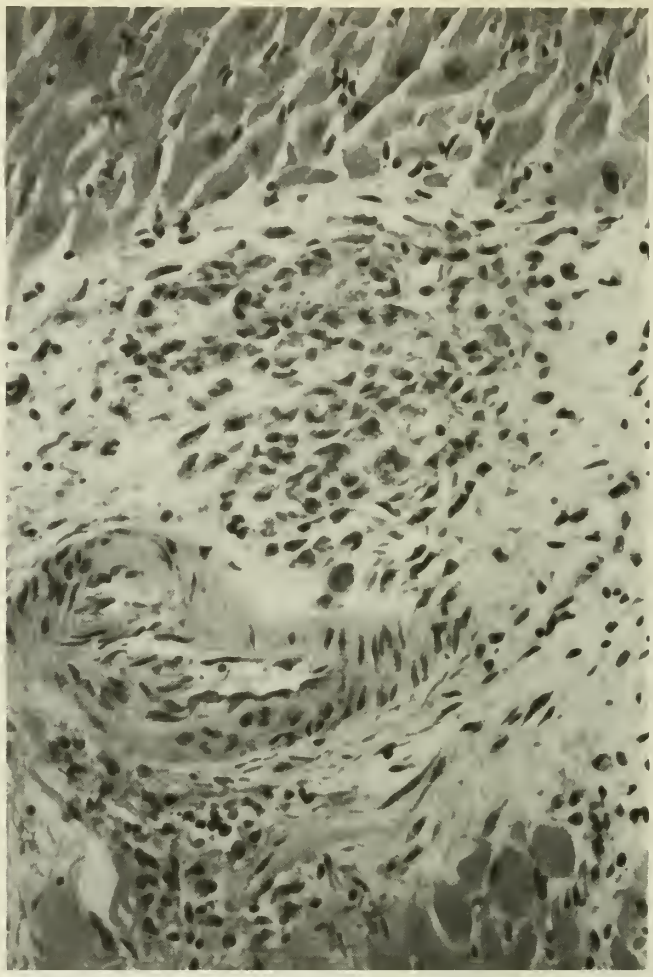


**Figure 5.**—Nodular accumulation of mononuclear cells forms the Aschoff body adjacent to a vessel in the interstitium (hematoxylin-eosin, × 200).

**Figure 6.**—The micrograph shows a typical Anitschkow's myocyte with a caterpillar-like shape to the nucleus (hematoxylin-eosin, × 450).

Sections of the left internal carotid artery revealed an adherent thrombus composed of fibrin, platelets and scattered mononuclear cells. Sections of the softened areas of the left cerebral hemisphere showed focal areas of necrosis with macrophage response and surrounding scattered astrocytes. The lesion in the right putamen was more recent with eosinophilic shrunken neurons and no macrophage response.

These gross and microscopic findings confirmed a diagnosis of acute rheumatic myocarditis with a mural thrombus of the left ventricle. This led to both left and right carotid embolization with secondary infarction of the brain.

This case was a diagnostic problem for the clinicians. Although the clinical course suggested the heart as the source of the emboli, the studies done to evaluate cardiac disease did not substantiate an obvious heart lesion. Rheumatic fever has been an elusive diagnosis in the past and still presents diagnostic difficulties.[19] This is especially true in an era when acute rheumatic fever continues to decrease in incidence in the United States.[20,21] It is interesting to note that there has been a recent increase in the incidence of rheumatic fever in the state of Utah. Although this patient had two of the minor criteria for rheumatic fever—that is, arthralgias and fever—the carditis as one of the major criteria was not proved until after death. Migrating arthritis with swelling and inflammation of the joints was not recorded in this patient, although this is a common manifestation of the disease. The other major criteria—erythema marginatum, subcutaneous nodules and chorea—are less common and the last two are usually seen in children. This case does show that extensive interstitial myocardial disease may be present without detectable electrical or echocardiographic abnormalities. The early disease in this patient, although widespread, had not affected the ability of the heart to function. There was no evidence at autopsy of cardiac failure. His death could have been due to an acute arrhythmia but was most likely due to the cerebral infarctions with secondary brain swelling. The inability of the two-dimensional echocardiogram to show the apical thrombus in the left ventricle is significant. It is known that echocardiograms may miss mural thrombi simply because of their small size, but perhaps the location and the ability to separate the thrombus, especially at the apex, from the heart wall play an important role in their detection.[18] The thrombus in this case was relatively large and must have been obscured by the apical heart muscle. It is unfortunate that the use of heparin, which is the treatment of choice in patients with mural thrombi, did not prevent further embolization.

This case again emphasizes the need to consider the diagnosis of acute rheumatic fever in younger patients presenting with embolic phenomena after the more common causes of emboli have been eliminated.[22]

#### REFERENCES


1. Kurtzke JF: Epidemiology of cerebrovascular disease, chap 1, *In* McDowell FH, Caplan LR (Eds): Cerebrovascular Survey Report. National Institute of Neurological and Communicative Disorders and Stroke, 1985, pp 1-34

2. Burke JM, Schaberg DR: Neurosyphilis in the antibiotic era. Neurology 1985; 35:1368-1371

3. Mayeux R, Fahn S: Strokes and ulcerative colitis. Neurology (Minneap) 1978; 28:571-574

4. Rao KC, Knipp HC, Wagner EJ: Computed tomographic findings in cerebral sinus and venous thrombosis. Radiology 1981; 140:391-398

5. Adams HP, Butler MJ, Biller J, et al: Nonhemorrhagic cerebral infarction in young adults. Arch Neurol 1986; 43:793-796

6. Nadeau SE, Watson RT: Neurologic manifestations of vasculitis and collagen vascular syndromes, chap 59, *In* Baker AB, Joynt RJ (Eds): Clinical Neurology. Philadelphia, Harper & Row, 1985, pp 12-21, 68-72

7. Cupps TR, Moore PM, Fauci AS: Isolated angiitis of the central nervous system—Prospective diagnostic and therapeutic experience. Am J Med 1983; 74:97-105

8. Fisher CM, Ojemann RG, Roberson GH: Spontaneous dissection of cervicocerebral arteries. Can J Neurol Sci 1978; 5:9-19

9. O'Dwyer JA, Moscow N, Trevor R, et al: Spontaneous dissection of the carotid artery. Radiology 1980; 137:379-385

10. Houser OW, Mokri B, Sundt TM Jr, et al: Spontaneous cervical cephalic arterial dissection and its residuum: Angiographic spectrum. AJNR 1984; 5:27-34

11. Hart RG, Easton JD: Dissections of cervical and cerebral arteries. Neurol Clin 1983; 1:155-182

12. Barnett HJM: Heart in ischemic stroke—A changing emphasis. Neurol Clin 1983; 1:291-315

13. Barnett HJM: Cardiac causes of cerebral ischemia, chap 11, *In* Toole JF (Ed): Cerebrovascular Disorders. New York, Raven Press, 1984, pp 168-186

14. Greenlee JE, Mandell GL: Neurological manifestations of infective endocarditis: A review. Stroke 1973; 4:958-963

15. Pruitt AA, Rubin RH, Karchmer AW, et al: Neurologic complications of bacterial endocarditis. Medicine (Baltimore) 1978; 57:329-343

16. Amsterdam EA: Value and limitations of echocardiography in endocarditis. Cardiology 1984; 71:229-231

17. Lovett JL, Sandok BA, Giuliani ER, et al: Two-dimensional echocardiography in patients with focal cerebral ischemia. Ann Intern Med 1981; 95:1-4

18. Takamoto T, Kim D, Urie P, et al: Comparative recognition of left ventricular thrombi by echocardiography and cineangiography. Br Heart J 1985; 53:36-42

19. Tadzynski LA, Ryan ME: Diagnosis of rheumatic fever—A guide to the criteria and manifestations. Postgrad Med 1986; 79:295-300

20. Gillum RF: Trends in acute rheumatic fever and chronic rheumatic heart disease: A national perspective (Editorial). Am Heart J 1986; 111:430-432

21. Krause RM: Acute rheumatic fever: An elusive enigma. J Allergy Clin Immunol 1986; 77:282-290

22. Cerebral Embolism Task Force: Cardiogenic brain embolism. Arch Neurol 1986; 43:71-84

# Editorial Comment

## Stroke in Young People—The Heart of the Matter

ROBERT G. HART, MD, *and* GREGORY L. FREEMAN, MD, *San Antonio*

Not long ago, it was the conventional wisdom that ischemic strokes in young people were tragic curiosities of unfathomable cause and with a benign prognosis. New concepts of pathogenesis combined with diagnostic advances and careful study of large numbers of such patients have challenged these traditional views. In recent clinical series, a likely cause of brain infarction has been identified in 67% to 91% of young people with stroke.[1-5] In the past decade, several new causes of ischemic stroke have been recognized and other, previously known causes further defined and emphasized. Considerable attention has focused on arterial dissection, the prothrombotic state associated with lupus anticoagulants and especially embolism related to mitral valve prolapse and occult cardiac disorders.

Arterial dissections of the cervical carotid and vertebral arteries are an important cause of stroke in otherwise healthy young adults, accounting for 4% to 22% of brain infarcts.[1-3,6] Once believed to be quite rare, with only a handful of cases reported before 1975, several hundred cases of patients with dissections have been reported in the past decade. Dissection occurs when blood extrudes into the arterial wall, collecting subintimally or intramedially and resulting in compression of the true lumen. Unusual neck torsion or trauma, though often quite minor, precedes the onset of symptoms in many patients, particularly those with vertebral artery dissections.[6] The hallmark of cervical carotid artery dissection is prominent pain in the ipsilateral neck, face or head, coupled with brain ischemia in a relatively young person (mean age about 40 years). An ipsilateral partial Horner's syndrome (oculosympathetic paresis) is present in half of patients. Pathologic studies have failed to identify underlying arterial abnormalities predisposing to dissection in most patients, although fibromuscular dysplasia and related intimal abnormalities have been associated with multiple and recurrent dissections.

Recent interest and enthusiasm have led to erroneous overdiagnosis of cervical carotid artery dissection, based on nonspecific arteriographic abnormalities. The arteriographic features of carotid dissection have been recently reviewed.[6-9] As emphasized by Fisher and co-workers in 1978, a tapered occlusion of the cervical carotid artery is the least specific arteriographic abnormality and does not strongly suggest dissection unless reflux into the ipsilateral carotid siphon can be shown via collateral filling.[7] In our experience, emboli lodging at the internal carotid artery bifurcation are a more common cause of tapered cervical carotid artery occlusion (due to retrograde thrombosis) than are dissections. Any cause of distal carotid occlusion can produce this arteriographic abnormality.[6] Casual diagnosis of any and all unusual, nonspecific arterial lesions as dissection has led to frequent errors in management and considerable obfuscation in the literature.

The role of prothrombotic states as a cause of stroke in young people has long been postulated, but laboratory markers have been elusive.[10] Recent attention has focused on the association of lupus anticoagulants and related antiphospholipid antibodies with otherwise unexplained thrombosis, both venous and arterial.[1,11-13] Lupus anticoagulant is a double misnomer. Although initially characterized in patients with systemic lupus, most patients who harbor these antibodies do not have the disease. While these antibodies cause the activated partial thromboplastin time (APTT) to be prolonged in vitro, they are associated with thrombosis, not bleeding, in vivo. The antibodies responsible for the prolongation of the APTT, the conventional laboratory marker of lupus anticoagulant, appear to be a subset of a larger, heterogeneous group of antiphospholipid antibodies that are also associated with thrombosis. Young adults with otherwise unexplained stroke have been described who do not have lupus anticoagulants (defined by abnormal results of an APTT dilution test) but who do have antiphospholipid antibodies.[13] Further exploration of the association between antiphospholipid antibodies and unexplained stroke is needed to define whether a causal relation exists and, if so, the mechanism, natural history and optimal treatment.

Cardiogenic embolism accounts for about a third of strokes in young people.[1] While the cardioembolic source is often apparent, it may be occult.[1,2,14-16] A diagnosis of cardiogenic brain embolism is difficult to establish with certainty when the embolic source is inapparent, requiring a constellation of clinical features, none of which is individually specific.[17,18] The abrupt onset of the maximal neurologic deficit, sometimes associated with a transient loss of consciousness, is suggestive of cardioembolic stroke. Multiple cortical brain infarcts in different arterial distributions, especially if found to be hemorrhagic on computed tomographic scans, support a cardioembolic stroke mechanism.[17] Serial arteriography, if initially carried out within 24 to 48 hours of stroke onset, can occasionally demonstrate migration of embolic fragments, the most specific clinical feature. The lack of diagnostic features that are highly specific or quantitatively validated is a major, unresolved clinical problem. The diagnosis of cardioembolic stroke has often been missed.[19] New diagnostic techniques to image cardiac thrombi or cardiac disorders predisposing to thrombi (or both) have allowed improved detection of occult embolic sources and more accurate diagnosis.[16,20-23]

Mitral valve prolapse has been associated with ischemic stroke in young adults.[17,24] The presumed mechanism is em-

(Hart RG, Freeman GL: Stroke in young people—The heart of the matter. West J Med 1987 May; 146:596-597)

From the Department of Medicine, University of Texas Health Science Center, San Antonio.
Reprint requests to Robert G. Hart, MD, Department of Medicine, University of Texas Health Science Center, 7703 Floyd Curl Dr, San Antonio, TX 78284.

bolism of aseptic thrombi that form on the fissured surface of the myxomatous and redundant valve leaflets; a cardioembolic mechanism is supported by the handful of autopsied cases.[25,26] Mitral valve prolapse is a common disorder in healthy young people without stroke, present in about 5% of men and as many as 15% of young women, depending on echocardiographic criteria.[27] While the risk of ischemic stroke is increased in young adults with mitral valve prolapse, the absolute risk remains very low (estimated at 1 stroke per 5,000 young people per year), and no antithrombotic prophylaxis is warranted in asymptomatic young adults with mitral valve prolapse.[28] Similarly, when a young adult with ischemic stroke is found to have mitral valve prolapse, a cause-effect cannot be assumed until other causes of stroke have been vigorously excluded. Even then, the diagnosis should be viewed with skepticism, as mitral valve prolapse is coincidental in about half of young adults with stroke who harbor this common condition. No auscultatory or echocardiographic features have yet been elucidated that distinguish embolism-prone mitral valve prolapse from the more common benign form. Preliminary observations suggest that thickening of the leaflets and concomitant aortic valve prolapse may be predictive.[29] In young adults with an initial stroke attributed to mitral valve prolapse, the risk of recurrent stroke is surprisingly low,[30] although in a few patients recurrent emboli and progressive valvular insufficiency may necessitate valve replacement.[31]

In young stroke victims with no clear cause of stroke following initial diagnostic testing, what further cardiac investigations should be done? Two-dimensional echocardiography sensitively detects large ventricular thrombi, but is less useful for small ventricular thrombi and thrombi in the atrial appendage.[32,33] Small (2 to 4 mm) thrombi in the ventricular apex, especially if they have a flat, plaquelike configuration, are easily missed by echocardiography, but yet can embolize to cause devastating strokes. Wall-motion abnormalities are often apparent when thrombi are too small to be directly visualized. Transesophageal echocardiography appears to allow detection of atrial thrombi not visualized by standard techniques.[33] The relative sensitivity of magnetic resonance imaging[23] and isotope-labeled platelet studies[20] compared with echocardiography is not yet fully defined. Contrast echocardiography will detect atrial septal defects that can underlie paradoxical embolism.[21,34,35]

When imaging techniques fail to detect a possible cardioembolic source, prolonged and repeated ambulatory monitoring of cardiac rhythm to detect paroxysmal atrial fibrillation is indicated, especially if palpitations occur or if left atrial enlargement is present. Chest x-ray films should be carefully evaluated for the presence of arteriovenous malformations. Even with vigorous efforts, some cardioembolic sources defy diagnosis. The small lesions of nonbacterial thrombotic (marantic) endocarditis usually are located on the atrial surface of the mitral valve and are notoriously difficult to detect echocardiographically. Early cardiomyopathies can present with embolism, despite normal electrocardiograms and echocardiograms.[15]

Should empiric treatment with anticoagulants be initiated for young people with ischemic stroke in whom embolism is suspected but in whom no cardioembolic source can be defined? When ischemia is recurrent and associated with features suggestive of embolism, anticoagulation should be considered, despite the uncertainties inherent in this situation. Frequent, thorough reevaluation should be undertaken in such patients, seeking definition of the stroke mechanism.

Stroke in young people is an uncommon problem. Establishing the cause of stroke is important, allowing specific therapy to minimize recurrent brain ischemia. Several newly recognized mechanisms of stroke that have been defined in young patients are known to affect all age groups. Cardioembolic sources are often occult, but have important treatment implications. When the cause of ischemic stroke in a young person is unclear after a thorough initial diagnostic evaluation, it is worthwhile to take a second look at the heart.

#### REFERENCES


1. Hart RG, Sherman DG, Miller VT, et al: Ischemic stroke in young adults. Curr Probl Cardiol 1983; 8:43-52
2. Adams HP, Butler MJ, Biller J, et al: Nonhemorrhagic cerebral infarction in young adults. Arch Neurol 1986; 43:793-796
3. Hilton-Jones D, Warlow CP: The causes of stroke in the young. J Neurol 1985; 232:137-143
4. Klein GM, Seland TP: Occlusive cerebrovascular disease in young adults. Can J Neurol Sci 1984; 11:302-304
5. Grindal AB, Cohen RJ, Saul RF, et al: Cerebral infarction in young adults. Stroke 1978; 9:39-42
6. Hart RG, Easton JD: Dissections of cervical and cerebral arteries. Neurol Clin 1983; 1:155-182
7. Fisher CM, Ojemann RG, Roberson GH: Spontaneous dissection of cervico-cerebral arteries. Can J Neurol Sci 1978; 5:9-19
8. Hart RG, Easton JD: Dissections and trauma of cervico-cerebral arteries, *In* Barnett HJM, Stein BM, Mohr JP, et al (Eds): Stroke. New York, Churchill-Livingstone, 1986, pp 775-788
9. Mokri B, Sundt TM, Houser OW, et al: Spontaneous dissection of the cervical internal carotid artery. Ann Neurol 1986; 19:126-138
10. Schafer AI: The hypercoagulable states. Ann Intern Med 1985; 102:814-820
11. Hart RG, Miller VT, Coull BM, et al: Cerebral infarction associated with lupus anticoagulants—Preliminary report. Stroke 1984; 15:114-118
12. Levine SR, Welch KMA: Cerebrovascular ischemia associated with lupus anticoagulant. Stroke 1987; 18:257-263
13. Coull BM, Bourdette D, Goodnight S, et al: Multiple cerebral infarctions associated with antibodies to cardiolipins. Neurology 1986; 36:252
14. Biller J, Johnson MR, Adams HP, et al: Echocardiographic evaluation of young adults with nonhemorrhagic cerebral infarction. Stroke 1986; 17:608-612
15. Rice GPA, Ebers GC, Newland F, et al: Recurrent cerebral embolism in cardiac amyloidosis. Neurology (Minneap) 1981; 31:904-906
16. Rem JA, Hachinski VC, Boughner DR, et al: Value of cardiac monitoring and echocardiography in TIA and stroke patients. Stroke 1985; 16:950-956
17. Cerebral Embolism Task Force: Cardiogenic brain embolism. Arch Neurol 1986; 43:71-84
18. Ramirez-Lassepas M, Cipolle RJ, Bjork RJ, et al: Can embolic stroke be diagnosed on the basis of neurologic clinical criteria? Arch Neurol 1987; 44:87-89
19. Humphrey PRD, Harrison MJG: How often can an embolic stroke be diagnosed clinically? A clinicopathological correlation. Postgrad Med J 1985; 61:1039-1042
20. Kessler C, Henningsen H, Reuther R, et al: Identification of intracardiac thrombi in stroke patients with indium-111 platelet scintigraphy. Stroke 1987; 18:63-67
21. Goldstein JA, Schiller NB, Lipton MJ, et al: Evaluation of left ventricular thrombi by contrast-enhanced computed tomography and two-dimensional echocardiography. Am J Cardiol 1986; 57:757-760
22. Harvey JR, Teague SM, Anderson JL, et al: Clinically silent atrial septal defects with evidence for cerebral embolization. Ann Intern Med 1986; 105:695-697
23. Higgins CB, Lanzer P, Stark D, et al: Imaging by nuclear magnetic resonance in patients with chronic ischemic heart disease. Circulation 1984; 69:523-531
24. Barnett HJM, Boughner DR, Taylor DW, et al: Further evidence relating mitral valve prolapse to cerebral ischemic events. N Engl J Med 1980; 302:139-144
25. Cerebral Embolism Study Group: Cardioembolic stroke, early anticoagulation, and brain hemorrhage. Arch Intern Med 1987, in press
26. Schnee MA, Bucal AA: Fatal embolism in mitral valve prolapse. Chest 1983; 83:285-287
27. Savage DD, Garrison RJ, Devereaux RB, et al: Mitral valve prolapse in the general population—1. Epidemiologic features: The Framingham Study. Am Heart J 1983; 106:571-576
28. Hart RG, Easton JD: Mitral valve prolapse and cerebral infarction. Stroke 1982; 13:429-430
29. Barletta GA, Gagliardi R, Benvenuti L, et al: Cerebral ischemic attacks as a complication of aortic and mitral valve prolapse. Stroke 1985; 16:219-223
30. Jackson AC, Boughner DR, Barnett HJM: Mitral valve prolapse and cerebral ischemic events in young adults. Neurology (NY) 1984; 34:784-787
31. Hanson MR, Conomy JP, Hodgman JR: Brain events associated with mitral valve prolapse. Stroke 1980; 11:499-506
32. Meltzer RS, Visser CA, Fuster V: Intracardiac thrombi and systemic embolization. Ann Intern Med 1986; 104:689-698
33. Aschenberg W, Schluter M, Kremer P, et al: Transesophageal two-dimensional echocardiography for the detection of left atrial appendage thrombus. J Am Coll Cardiol 1986; 7:163-166
34. Ginzton LE, French WR, Mena I: Combined echocardiographic and radionuclide diagnosis of atrial septal defect: Accuracy of the technique and analysis of erroneous diagnoses. Am J Cardiol 1984; 53:1639-1642
35. Jones HR, Caplan LR, Come PC, et al: Cerebral emboli of paradoxical origin. Ann Neurol 1983; 13:314-319

# Medical Staff Conference

## Acute Pancreatitis

*These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs Homer A. Boushey, Associate Professor of Medicine, and David G. Warnock, Associate Professor of Medicine, under the direction of Dr Lloyd H. Smith, Jr, Professor of Medicine and Associate Dean in the School of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, School of Medicine, San Francisco, CA 94143.*

RICHARD K. ROOT, MD:* *Acute pancreatitis is still a common medical condition that may be life-threatening in severity, as represented by the case presented herein, and can produce considerable and recurring morbidity. While insights have been gained into pathogenetic mechanisms, and management of some complications such as pseudocyst has been aided by new imaging techniques, much remains to be learned. The illustrative case and the discussion by James Grendell, MD, Assistant Professor of Medicine at the University of California, San Francisco (UCSF), and San Francisco General Hospital Medical Center, bring us up-to-date on this important subject.*

JAMES EGAN, MD:† The patient, a 57-year-old man, was brought to the UCSF emergency department after being found on the floor of his home. He had been last seen two days before by his landlord. The patient was initially oriented, but had progressively declining mental status en route, with a systolic blood pressure of 60 mm of mercury by palpation. No medical history was known.

On physical examination he was obese and minimally arousable. Blood pressure was 60/40 mm of mercury and increased to 90/60 mm of mercury after an infusion of 6 liters of a normal saline solution and administration of dopamine hydrochloride. Pulse was 120 per minute, respiratory rate was 14 and temperature was 35.9°C (96.6°F). He had anicteric sclerae, equal, round and reactive pupils, no papilledema and dry mucous membranes. His neck was supple, there was no lymphadenopathy and his lungs were clear. The findings of a cardiac examination were normal, without gallops, murmurs or rubs, and the jugular veins were flat. Pulses were symmetric, with an absent dorsalis pedis pulse bilaterally. The abdomen was obese and nonrigid with diminished bowel sounds and diffuse tenderness to direct palpation, but no evidence of peritoneal signs. Liver span was 11 cm; there was no splenomegaly or ecchymosis of the flanks or abdomen. The rectal examination was notable for impacted stool with a trace of occult blood. Extremities were cool without edema. On neurologic examination there were no focal abnormalities and no asterixis. The skin had pronounced tenting; there were no spider angiomas.

The chest radiograph showed no abnormalities. Laboratory studies elicited the following values: hemoglobin 15 grams per dl; leukocyte count 14,000 per μl (80% polymorphonuclear leukocytes, 15% bands); platelets 148,000 per μl; prothrombin time 11.8 seconds, and partial thromboplastin time 25.2 seconds. Serum electrolyte levels were as follows: sodium 158, potassium 4.4, chloride 122 and bicarbonate 9 mEq per liter. Blood urea nitrogen (BUN) level was 83, creatinine 4.2, glucose 1,260 and calcium 9 mg per dl; serum amylase 1,125 IU per liter; creatine kinase 10,000 units per liter, lactic dehydrogenase 580 units per liter; normal triglyceride levels; osmolality 430 mosm per kg water. Analysis of a urine specimen showed trace protein, 4+ glucose, no ketones and normal sediment. Arterial blood gas determinations made while the patient was breathing 100% oxygen by mask were as follows: pH 7.12, partial carbon dioxide pressure 33 torr and partial oxygen pressure ($Po_2$) 80 torr. The electrocardiogram showed no acute changes.

A central venous line was placed, and the patient was given 8 liters of a normal saline solution, but he continued to require vasopressors for hypotension. An abdominal ultrasound study showed an enlarged pancreas and increased echogenicity of the liver, but a normal spleen, biliary system and kidneys. Radiographs of the kidneys, ureters and bladder and an upright film of the abdomen were unremarkable. A regimen of broad-spectrum antibiotics was started and an endotracheal tube inserted because of persistent hypoxemia and acidemia. A repeat chest radiograph was normal and the $Po_2$ with the patient receiving 100% forced inspiratory oxygen was 60 torr. The patient continued to have oliguria throughout, with progressive elevation of the BUN and creatinine levels. Several hours after admission, repeat laboratory values included a serum sodium level of 159, potassium 4.0 and chloride 130 mEq per liter; calcium 6.5 mg per dl; albumin level normal; bicarbonate 15 mEq per liter; phosphorus 3.2 mg per dl; glucose 300 to 400 mg per dl.

The patient was taken to the operating room because of persistent acidemia and a tentative diagnosis of possible bowel infarction. Operative findings included nonhemorrhagic pancreatitis with saponification, macronodular cirrhosis and many liters of clear ascitic fluid. The patient required vasopressor support postoperatively and had no improvement in his neurologic state. He died less than 24 hours after the surgical procedure.

JAMES H. GRENDELL, MD:‡ Acute pancreatitis is an inflammatory process of variable severity ranging from a mild,

*Professor and Chair, Department of Medicine, UCSF School of Medicine.

†Resident, UCSF School of Medicine.

‡Assistant Professor of Medicine and Physiology, UCSF Gastrointestinal Unit; San Francisco General Hospital Medical Center.

(Grendell JH, Egan J: Acute pancreatitis [Medical Staff Conference]. West J Med 1987 May; 146:598-602)

ABBREVIATIONS USED IN TEXT

BUN = blood urea nitrogen
CT = computed tomography
ERCP = endoscopic retrograde cholangiopancreatography
$Po_2$ = partial pressure of oxygen
UCSF = University of California, San Francisco

self-limited form with interstitial edema of the pancreas and peripancreatic fat necrosis to a severe form with extensive hemorrhagic necrosis of the pancreas, intrapancreatic and peripancreatic fat necrosis and a potentially fatal outcome. The frequency of acute pancreatitis in the United States has been estimated at about 5,000 new cases per year.[1]

## Etiology

Various etiologic factors have been associated with the development of acute pancreatitis (Table 1), but two causes—chronic alcohol abuse and gallstone disease—are responsible for 75% to 80% of cases in most series. The various etiologic factors can be grouped into three categories (Table 1):

- *Mechanical.* These involve either obstruction of or damage to the pancreatic duct system as the primary event leading to pancreatic injury.
- *Metabolic.* These appear to involve pathologic alterations in the metabolic and secretory processes of the pancreatic secretory cell, the acinar cell, as the precipitating event.
- *Other.* These include infections, ischemic injury due to vasculitis and idiopathic factors (5% to 10% of cases in most series).

## Pathogenesis

The manner in which acute pancreatitis is produced is not known with certainty for any of the etiologic factors. Various plausible mechanisms have been proposed, however. In gallstone pancreatitis, transient impaction of a gallstone in the distal common bile duct or at the duodenal papilla may produce reversal of the normal pressure gradient (pressure in the pancreatic duct is greater than pressure in the bile duct which is greater than pressure in the duodenum), leading to either rupture of the pancreatic ducts or reflux of bile or duodenal juice into the pancreas. Support for this view comes from studies showing recovery of gallstones from the stools of a high percentage of nonalcoholic patients presenting with acute pancreatitis.[2] Pancreatitis due to blunt or penetrating abdominal trauma or following endoscopic retrograde cholangiopancreatography (ERCP) is likely due to traumatic disruption of the pancreatic duct system. Chronic alcohol abuse has been estimated to increase the risk of pancreatitis almost 20-fold.[3 (p7)] Although chronic ethanol ingestion has been shown to produce changes in the composition of pancreatic juice in humans, such as an increase in trypsinogen, the proenzymatic form of trypsin, relative to trypsin inhibitor,[4] how chronic alcohol abuse leads to acute pancreatitis remains unknown. The pancreatitis associated with hyperlipoproteinemias characterized by substantially elevated serum triglyceride concentrations (often in the range of 1,000 mg per dl or more) has been attributed to the action of circulating pancreatic lipase on plasma triglycerides leading to the production of fatty acids toxic to pancreatic tissue.[5] Poisoning by scorpion venom and organic phosphate insecticides mimics the effects of physiologic stimuli of pancreatic secretion and may damage the acinar cells by hyperstimulation.[6,7]

## Pathophysiology

Whatever the etiologic factor involved, acute pancreatitis is in effect an "autodigestion" of the gland produced by premature activation of digestive enzymes leading to damage and necrosis of the enzyme-secreting (acinar) cells. The activation of trypsinogen to trypsin appears to be of central importance in that trypsin can activate all the pancreatic enzymes—including trypsinogen—secreted as proenzymes (zymogens). The initial damage to acinar cells results in the release and activation of more digestive enzymes, setting up a "vicious cycle." If the inflammatory process extends beyond the pancreas, it can lead to retroperitoneal and peritoneal fat necrosis, hemorrhage due to disruption of blood vessels, exudation of peritoneal fluid, disturbances of gastric and intestinal motility (ileus) due to irritation or disruption of nerves coursing through the mesentery and obstruction of flow in the common bile duct.

Activated pancreatic trypsin can also activate complement and convert kallikrein to bradykinin and plasminogen to plasmin. These substances—and probably others not yet identified—can contribute to both the local inflammatory process in and around the pancreas and the systemic manifestations

TABLE 1.—*Major Etiologic Factors in Acute Pancreatitis*

| |
|---|
| *Mechanical* |
| Gallstone disease |
| Abdominal trauma |
| Surgical procedure |
| Endoscopic retrograde cholangiopancreatography |
| Parasitic disease—ascariasis, clonorchiasis |
| Pancreatic duct obstruction by tumor or by inflammatory diseases of the duodenum or ampulla of Vater |
| Pancreas divisum |
| *Metabolic* |
| Chronic alcohol abuse |
| Hyperlipoproteinemia |
| Drugs, such as azathioprine, furosemide |
| Scorpion venom |
| Organophosphate insecticides |
| Hereditary |
| ? Hypercalcemia |
| *Other* |
| Infections—mumps, coxsackievirus, ? hepatitis B, ? mycoplasma |
| Vasculitis—systemic lupus erythematosus, thrombotic thrombocytopenic purpura, Henoch-Schoenlein purpura, polyarteritis nodosa |
| Idiopathic |

TABLE 2.—*Conditions Other Than Acute Pancreatitis That Can Produce an Elevation in Serum Amylase Concentration*

| |
|---|
| Renal failure |
| Diabetic ketoacidosis |
| Common bile duct obstruction |
| Penetrating duodenal ulcer |
| Perforation of esophagus, stomach, intestine |
| Intestinal ischemia |
| Salivary gland disease |
| Chronic alcoholism |
| Opiate administration |
| Surgical procedure |
| Severe burns |
| Malignant tumors, such as of pancreas or lung |
| Gynecologic disorders, such as ruptured ectopic pregnancy or ovarian cyst |

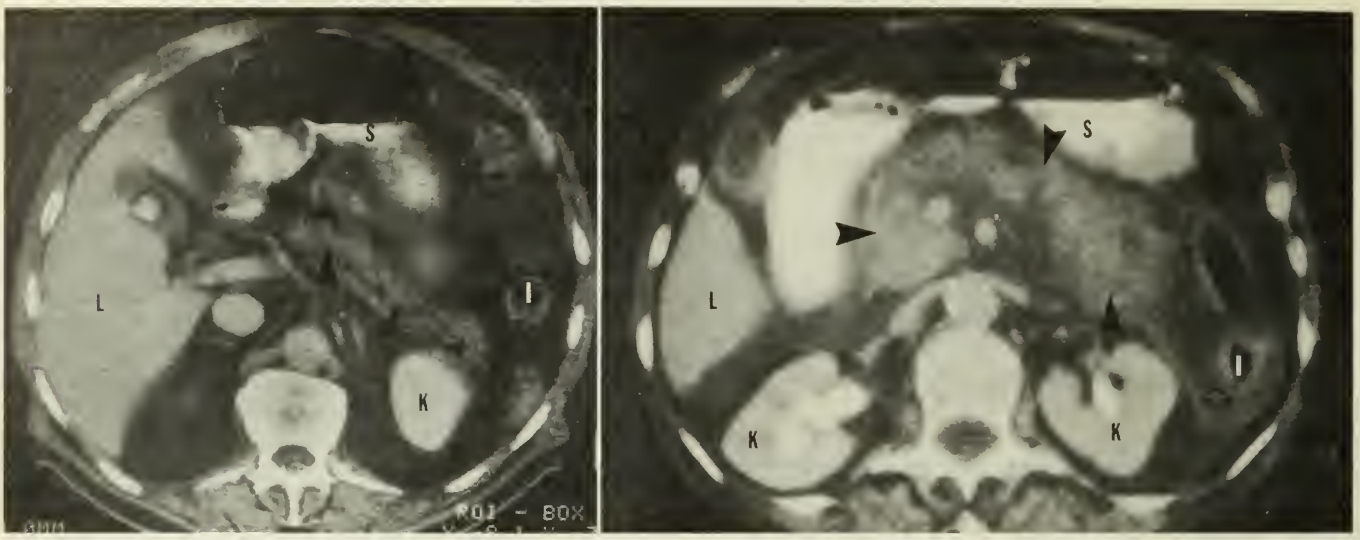



**Figure 1.**—Findings on computed tomography (CT) in acute pancreatitis. **Left,** Normal pancreas. Note that the pancreas **(solid arrows)** is a thin, relatively uniform organ that is clearly demarcated from surrounding structures. Other labeled organs are liver **(L)**, stomach **(S)**, left kidney **(K)** and a loop of intestine **(I)**. **Right,** Acute pancreatitis. Note that the pancreas **(solid arrows)** is greatly and irregularly enlarged and is displacing the stomach **(S)** anteriorly. In addition, inflammation has extended beyond the pancreas to involve the left anterior pararenal space **(open arrow)** and to surround a loop of intestine **(I)**. Other labeled organs are liver **(L)** and kidneys **(K)**.

such as metabolic abnormalities—hypocalcemia, hyperglycemia—coagulopathy and renal or pulmonary insufficiency.

Although acute pancreatitis most often resolves spontaneously, death may occur, usually due to hypovolemic shock, renal or pulmonary insufficiency, pancreatic abscess or sepsis.[8]

## Diagnosis

About 95% of patients with acute pancreatitis present with abdominal pain that in about half will be upper abdominal pain radiating to the back. Nausea and vomiting are present in 60% to 90% of patients. On physical examination abdominal tenderness or guarding or both are noted in 80% to 90% of patients, distention and tympany in 70% and elevated temperature (usually < 39°C [102°F]) in 50% to 80%. The presence of a temperature higher than 39°C should suggest cholecystitis, cholangitis, peritonitis or intra-abdominal abscess as alternative or additional diagnoses.

The clinical diagnosis of acute pancreatitis requires laboratory or radiologic confirmation because the symptoms and signs are nonspecific. A perforated ulcer, cholecystitis or cholangitis and intestinal ischemia can present in a similar fashion. Measurement of the concentration of the pancreatic enzyme amylase in serum (or, at times, in urine) has been the most widely used diagnostic study for confirming the diagnosis of pancreatitis. Although the serum concentration of amylase is elevated in most patients with acute pancreatitis at the time of presentation, it may be normal (falsely negative) if not measured within two to seven days of the onset of symptoms and is normal in 10% to 30% of patients with acute pancreatitis on the basis of chronic alcohol abuse.[9] Falsely positive results (elevation in serum amylase) may occur in a variety of circumstances, some of which can mimic the clinical presentaton of acute pancreatitis (Table 2). Because of the possibility of both false-positive and false-negative amylase determinations, various other laboratory tests have been or are being evaluated. These include the measurement of the amylase-to-creatinine clearance ratio and the determination of the serum concentrations of pancreatic isoamylase or of other pancreatic enzymes such as lipase, trypsin, elastase and phospholipase A. So far, however, none of these other laboratory tests have been convincingly shown to improve on the diagnostic accuracy of measuring the serum amylase concentration.[10]

The most important recent advance in the diagnosis of acute pancreatitis has been the development of abdominal sonography and, especially, computed tomography (CT) as imaging modalities. When the diagnosis remains in doubt following clinical assessment and serum amylase determination, especially in a severely ill patient, these diagnostic techniques are very helpful in confirming the diagnosis of acute pancreatitis and excluding other intra-abdominal catastrophic processes (Figure 1).[11] Abdominal sonography, however, often cannot be accurately done in patients with a moderate to severe ileus, and computed tomography is the imaging procedure of choice in that setting.

Although mild edematous pancreatitis may not produce changes identifiable by sonography or CT, the absence of sonographic or CT abnormalities in the pancreas or surrounding tissue essentially excludes acute pancreatitis as the cause of a catastrophic abdominal process. But because the abnormal findings may persist for an indefinite period of time following clinical resolution of acute pancreatitis, one may obtain a "false-positive" sonogram or CT scan. That is, a patient with a previous episode of acute pancreatitis that had resolved clinically who now has abdominal symptoms and findings unrelated to the pancreas may be wrongly diagnosed as having acute pancreatitis based on residual changes seen on abdominal sonography or CT.[12]

## Clinical Course

In the great majority of patients, acute pancreatitis resolves spontaneously with the return of normal pancreatic exocrine and endocrine function. Some patients, however, will have a much more complicated course. The overall mortality is generally less than 10%, is higher for first episodes than for recurrences and may be somewhat higher for patients with gallstone pancreatitis than with alcohol-related dis-

ease.[13] Major causes of death include hypovolemia and shock early in the course of the disease, organ system failure (primarily pulmonary and renal), pancreatic abscess and sepsis.[8] When pulmonary or renal failure complicate acute pancreatitis, mortality may exceed 50%.[14]

Considerable effort has been expended in identifying criteria for predicting the prognosis of patients with acute pancreatitis.[15] Currently, the most widely used in the United States are those of Ranson (Table 3),[13,16] which involve 11 objective findings determined either on admission or over the initial 48 hours of hospital stay. The number of signs present for a given patient is directly related to a patient's likelihood of having significant morbidity and of dying (Table 4). Other investigators have suggested a prognostic value for various other factors, including the serum concentraton of methemalbumin, albumin and ribonuclease; the volume and color of peritoneal fluid obtained by paracentesis, and CT findings.[15,17] Work from our institution has not confirmed a substantial prognostic value for CT findings.[18] In the care of an individual patient, I do not believe these various proposed means of predicting prognosis significantly improve on one's overall clinical assessment based on bedside evaluation and routine laboratory studies. They do, however, provide a means of categorizing the severity of illness in clinical study patient groups, which assists in the comparison of studies from different centers evaluating natural history or therapeutic interventions in acute pancreatitis.

## Management

There is no effective specific therapy for treating the underlying disease process in acute pancreatitis. Therefore, the therapeutic approach at present is one of supportive care and treatment of complications. The primary goal initially is to prevent or correct hemodynamic abnormalities by vigorously replacing volume deficits and electrolyte losses that can be massive and life-threatening.[19] Correction of hypocalcemia should be cautious because hypocalcemia in a patient with acute pancreatitis is rarely clinically significant. Patients may require substantial amounts of analgesia, usually with meperidine hydrochloride (Demerol). Oral intake should be prohibited until the patient's clinical condition improves, and nasogastric suction should be used for patients who are vomiting or who have significant abdominal distention.[20] A patient's degree of respiratory effort, chest findings and arterial blood gas values should be monitored closely, especially early in the hospital course. Evidence of hypoxemia on blood gas determination has been found in as many as 60% of patients admitted to hospital with acute pancreatitis, with respiratory failure developing in about 10%.[21,22] Oxygen and ventilatory support should be provided as needed.[23]

Various pharmacologic approaches to the treatment of acute pancreatitis have been attempted. The use of prophylactic antibiotics,[24] a protease (trypsin) inhibitor[25] and a variety of drugs to "put the pancreas at rest"—anticholinergics, glucagon, somatostatin, cimetidine, calcitonin[1,24,26]—has *not* been shown effective in clinical trials. The use of prostaglandins has been proposed as a possible treatment,[27] but their value remains unestablished.

An aggressive surgical approach involving debridement and drainage of the pancreas and surrounding tissue has been advocated in severe cases of acute pancreatitis.[13] The morbidity and mortality associated with such an approach, however, is high and its efficacy not shown in any controlled trial. Peritoneal lavage has also been used to remove potentially toxic products of pancreatic inflammation, but a recent prospective, randomized, controlled trial found no benefit either in terms of mortality or complications.[28] Currently there is considerable interest in whether early surgical or endoscopic removal of impacted gallstones would benefit patients who have gallstone pancreatitis.[29,30] Although a significant clinical benefit remains to be established in controlled trials, ERCP with papillotomy and stone extraction or nasobiliary drainage should be considered in patients with acute pancreatitis in the absence of a history of chronic alcohol abuse who fail to improve or, at least, clinically stabilize during the first 24 to 36 hours in hospital.

## Pancreatic Pseudocyst and Abscess

In patients with severe abdominal pain or an elevated serum amylase concentration persisting for more than a week, abdominal sonography or CT should be done to evaluate the possible formation of a pseudocyst (a collection of inflammatory debris and pancreatic secretion). In general, pseudocysts in patients with acute pancreatitis should be followed for at least six weeks before surgical intervention to allow either spontaneous resolution (about 25%)[31] or maturation of the pseudocyst wall to permit internal drainage to the stomach or small intestine. More urgent surgical intervention may be required if the pseudocyst wall ruptures into the peritoneal cavity or if the pseudocyst becomes infected, erodes into a blood vessel or produces protracted biliary or intestinal obstruction.

Patients having a temperature higher than 39°C, a leukocyte count greater than 20,000 per μl or clinical deterioration after initial improvement should be promptly evaluated for the presence of a pancreatic abscess by emergency CT and fine

TABLE 3.—*Ranson Criteria for Predicting Severity of Acute Pancreatitis**†

| |
|---|
| At admission or on diagnosis |
| Age > 55 years (over 70) |
| Leukocyte count > 16,000/μl (> 18,000) |
| Serum glucose level > 200 mg/dl (> 220) |
| Serum lactic dehydrogenase level > 350 IU/ml (> 400) |
| Serum aspartate aminotransferase level > 250 IU/dl |
| During initial 48 hours |
| Fall in hematocrit > 10% |
| Blood urea nitrogen level rise > 5 mg/dl (> 2) |
| Serum calcium level < 8 mg/dl |
| Base deficit > 4 mEq/liter (> 5) |
| Estimated fluid sequestration > 6 liters (> 4 liters) |
| Arterial $Po_2$ < 60 torr |

$Po_2$ = partial pressure of oxygen

*From Ranson.[13,16]

†When criteria values for nonalcoholic acute pancreatitis differ from those in alcohol-related disease, they are given in parentheses.

TABLE 4.—*Risk of Death or Major Morbidity Associated With Ranson Criteria of Severity in Acute Pancreatitis**

| *Criteria, No.* | *0-2* | *3-4* | *5-6* | *7-8* |
|---|---|---|---|---|
| Patients, No. | 347 | 67 | 30 | 6 |
| Mortality, % | 0.9 | 16 | 40 | 100 |
| Patients requiring > 7 days in intensive care unit, % | 2.9 | 24 | 53 | — |

*From Ranson.[13]

needle aspiration of any suspicious-looking fluid collections for Gram's stain and culture. If CT and results of a Gram's stain suggest the presence of a pancreatic abscess, a regimen of broad-spectrum antibiotics, such as ampicillin, gentamicin sulfate and metronidazole, should be started and the patient should undergo emergency surgical drainage of the suspected abscess. The mortality of pancreatic abscess untreated by surgical drainage approaches 100%. The earlier diagnosis and treatment resulting from the use of CT and fine needle aspiration have resulted in a reduction of mortality to less than 20%.[32,33]

## Preventing Recurrence

Recurrence of acute pancreatitis can be prevented in patients with gallstones by doing cholecystectomy and removing common duct stones, in patients with hyperlipoproteinemia by controlling serum triglyceride levels by diet and medication and in patients with drug-induced pancreatitis by removing the offending agent. The effect of abstaining from alcohol on the recurrence rate of alcohol-related acute pancreatitis has not been clearly established.

### REFERENCES


1. Toskes PP, Greenberger NJ: Acute and chronic pancreatitis. DM 1983; 29:1-81

2. Acosta JM, Ledesma CL: Gallstone migration as a cause of acute pancreatitis. N Engl J Med 1974; 290:484-487

3. Bradley EL III: Overview, *In* Complications of Pancreatitis—Medical and Surgical Management. Philadelphia, WB Saunders, 1982

4. Renner IG, Rinderknecht H, Valenzuela JE, et al: Studies of pure pancreatic secretions in chronic alcoholic subjects without pancreatic insufficiency. Scand J Gastroenterol 1980; 15:241-244

5. Havel RJ: Pathogenesis, differentiation, and management of hypertriglyceridemia. Adv Intern Med 1969; 15:117-154

6. Bartholomew C, McGeeney KF, Murphy JJ, et al: Experimental studies on the aetiology of acute scorpion pancreatitis. Br J Surg 1976; 63:807-810

7. Dressel TD, Goodale RL Jr, Arneson MA, et al: Pancreatitis as a complication of anticholinesterase insecticide intoxication. Ann Surg 1979; 189:199-204

8. Renner IG, Savage WT III, Pantoja JL, et al: Death due to acute pancreatitis—A retrospective analysis of 405 autopsy cases. Dig Dis Sci 1985; 30:1005-1018

9. Spechler SJ, Dalton JW, Robbins AH, et al: Prevalence of normal serum amylase levels in patients with acute alcoholic pancreatitis. Dig Dis Sci 1983; 28:86-89

10. Steinberg WM, Goldstein SS, Davis ND, et al: Diagnostic assays in acute pancreatitis—A study of sensitivity and specificity. Ann Intern Med 1985; 102:576-580

11. Lawson TL: Acute pancreatitis and its complications—Computed tomography and sonography. Radiol Clin North Am 1983; 21:495-513

12. Hill MC, Barkin J, Isikoff MB, et al: Acute pancreatitis: Clinical vs CT findings. AJR 1982; 139:263-269

13. Ranson JHC: Acute pancreatitis: Pathogenesis, outcome and treatmcnt. Clin Gastroenterol 1984; 13:843-863

14. Socrgel KH: Acute pancreatitis, *In* Sleisenger MH, Fordtran JS (Eds): Gastrointestinal Disease—Pathophysiology, Diagnosis, Management, 3rd Ed. Philadelphia, WB Saunders, 1983, pp 1462-1485

15. Williamson RCN: Early assessment of severity in acute pancreatitis. Gut 1984; 25:1331-1339

16. Ranson JHC: The timing of biliary surgery in acute pancreatitis. Ann Surg 1979; 189:654-663

17. Balthazar EJ, Ranson JHC, Naidich DP, et al: Acute pancreatitis: Prognostic value of CT. Radiology 1985; 156:767-772

18. Vernacchia FS, Jeffrey RB Jr, Federle MP, et al: Pancreatic abscess: Predictive value of abdominal CT. Radiology 1987; 162:435-438

19. Bradley EL III, Hall JR, Lutz J, et al: Hemodynamic consequences of severe pancreatitis. Ann Surg 1983; 198:130-133

20. Loiudice TA, Lang J, Mehta H, et al: Treatment of acute alcoholic pancreatitis: The roles of cimetidine and nasogastric suction. Am J Gastroenterol 1984; 79:553-558

21. Ranson JHC, Roses DF, Simon DF: Early respiratory insufficiency in acute pancreatitis. Ann Surg 1973; 178:75-79

22. Imrie CW, Ferguson JC, Murphy D, et al: Arterial hypoxia in acute pancreatitis. Br J Surg 1977; 64:185-188

23. Lankisch PG, Rahlf G, Koop H: Pulmonary complications in fatal acute hemorrhagic pancreatitis. Dig Dis Sci 1983; 28:111-116

24. Finch WT, Sawyers JL, Schenker S: A prospective study to determine the efficacy of antibiotics in acute pancreatitis. Ann Surg 1976; 183:667-671

25. Medical Research Council Multicentre Trial: Morbidity of acute pancreatitis: The effect of aprotinin and glucagon. Gut 1980; 21:334-339

26. Martinez E, Navarette F: A controlled trial of synthetic salmon calcitonin in the treatment of severe acute pancreatitis. World J Surg 1984; 8:354-359

27. Standfield NJ, Kakkar VV: Prostaglandins and acute pancreatitis—Experimental and clinical studies. Br J Surg 1983; 70:573-576

28. Mayer AD, McMahon MJ, Corfield AP, et al: Controlled clinical trial of peritoneal lavage for the treatment of severe acute pancreatitis. N Engl J Med 1985; 312:399-404

29. Mercer LC, Saltzstein EC, Peacock JB, et al: Early surgery for biliary pancreatitis. Am J Surg 1984; 148:749-753

30. Neoptolemos JP, London N, Slater ND, et al: A prospective study of ERCP and endoscopic sphincterotomy in the diagnosis and treatment of gallstone acute pancreatitis. Arch Surg 1986; 121:697-702

31. Bradley EL III, Clements JL Jr, Gonzalez AC: The natural history of pancreatic pseudocysts: A unified concept of management. Am J Surg 1979; 137:135-141

32. Bradley EL III, Fulenwider JT: Open treatment of pancreatic abscess. Surg Gynecol Obstet 1984; 159:509-513

33. Jeffrey RB Jr, Grendell JH, Federle MP, et al: Improved survival with early CT diagnosis of pancreatic abscess. Gastrointest Radiol 1987; 12:26-30

Epitomes
Important Advances in Clinical Medicine

# Emergency Medicine

*The Scientific Board of the California Medical Association presents the following inventory of items of progress in emergency medicine. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, research workers or scholars to stay abreast of these items of progress in emergency medicine that have recently achieved a substantial degree of authoritative acceptance, whether in their own field of special interest or another.*

*The items of progress listed below were selected by the Advisory Panel to the Section on Emergency Medicine of the California Medical Association and the summaries were prepared under its direction.*

Reprint requests to Division of Scientific and Educational Activities,
California Medical Association, PO Box 7690, San Francisco, CA 94120-7690

## Intraosseous Infusion for Emergency Vascular Access

ESTABLISHING INTRAVENOUS (IV) access in the resuscitation of an ill child is notoriously difficult. Peripheral veins may be collapsed, and often resuscitation is delayed while central intravenous access and vascular cutdowns are attempted. In contrast, intraosseous access is rapidly achieved and simple to do.

Intraosseous infusion of fluids and drugs has been described since the 1920s, and much laboratory and clinical investigation of its use was reported in the 1940s. In the 1950s, however, with the development of improved, disposable IV needles, intraosseous infusion was neglected. Only in the past few years has this technique been reevaluated as an alternative for intravascular access in a critically ill child.

Most authors recommend intraosseous entry on the anteromedial surface of the tibia 1 to 3 cm below the tibial tuberosity. Alternatively, the femur or distal tibia can be punctured. Needles with stylets, such as spinal or bone marrow needles, are preferred, but 18- or 20-gauge hypodermic needles may be used. Steady pressure or a screwing motion is used to traverse the bony cortex. Needle placement in the bone marrow is confirmed by a decrease in resistance during insertion, the ability to aspirate marrow and the free inflow of fluid. IV tubing is connected to the needle and drugs and fluids infused as needed.

Extensive marrow sinusoids empty into large medullary venous channels, which in turn drain into nutrient and emissary veins and return to the systemic circulation. Various studies in the 1940s have shown rapid entry of dyes, fluids and drugs from the bone marrow into the central circulation when the circulatory system is intact. More recent studies have shown the efficacy of this route during fibrillatory cardiac arrest in swine and hypotensive hemorrhage in calves. Any drug or fluid normally administered intravenously can be used intraosseously at comparable doses.

Complications are rare and include hematoma, subcutaneous infiltration and leakage from multiple puncture sites. Osteomyelitis has been described only with the infusion of hypertonic solutions or with long-term use of the intraosseous route. Fat or bone embolus has not been reported. Histologic and radiographic follow-up of involved bone does not show significant abnormality.

Intraosseous infusion is a safe, easy and reliable method of vascular access in an emergency situation.

JUDITH C. BRILLMAN, MD
*Stanford, California*

**REFERENCES**

Glaeser PW, Losek JD: Emergency intraosseous infusions in children. Am J Emerg Med 1986 Jan; 4:34-36

Parrish GA, Turkewitz D, Skiendzielewski JJ: Intraosseous infusions in the emergency department. Am J Emerg Med 1986 Jan; 4:59-63

Rosetti VA, Thompson BM, Miller J, et al: Intraosseous infusion: An alternative route of pediatric intravascular access. Ann Emerg Med 1985 Sep; 14:885-888

Shoor PM, Berryhill RE, Benumof JL: Intraosseous infusion: Pressure-flow relationship and pharmacokinetics. J Trauma 1979 Oct; 19:772-774

Spivey WH, Lathers CM, Malone DR, et al: Comparison of intraosseous, central and peripheral routes of sodium bicarbonate administration during CPR in pigs. Ann Emerg Med 1985 Dec; 14:1135-1140

## Sodium Bicarbonate Therapy in Cardiac Arrest

TRADITIONAL MEDICAL THERAPY for patients with cardiac arrest has included the use of sodium bicarbonate to reverse arterial acidosis. Previously, early administration of bicarbonate in the algorithms of advanced cardiac life support (ACLS) courses has led to its widespread use during resuscitation efforts. This occurred despite warnings in the textbook describing adverse effects of the use of bicarbonate.

In recent years mounting evidence has made these concerns more prominent. A closer study of blood chemistry has shown that arterial blood determinations fail to adequately reflect severe respiratory acidosis on the venous side. Moreover, a direct correlation between extracellular and intracellular pH does not exist. Several animal models have shown poorer results with bicarbonate infusion for lactic acidosis than with infusing saline solution alone.

Several mechanisms account for these observations. Infusing bicarbonate generates carbon dioxide ($CO_2$). With inadequate ventilation or excessive bicarbonate infusion, $CO_2$ levels rise rapidly, creating a respiratory acidosis. $CO_2$ rapidly diffuses across the cell membranes to cause intracellular acidosis. Myocardial function becomes depressed

when there is increased intracellular carbon dioxide tension. $CO_2$ diffuses across the blood-brain barrier more readily than does bicarbonate. Thus, a paradoxical cerebrospinal fluid acidosis occurs, which tends to depress respiration further.

Other adverse effects of sodium bicarbonate administration include a rise in serum osmolality, which may worsen the acidosis, and a shifting of the oxyhemoglobin dissociation curve. This leftward shift results in an increased affinity for oxygen and decreased unloading to the cells.

Adequate ventilation early in cardiac arrest states may prevent significant acidosis for about 30 minutes. Hyperventilation alone, therefore, is the initial therapy in arrest states. The use of bicarbonate therapy should be guided by arterial blood gas determinations in a patient with profound metabolic acidosis, and only when there is proper ventilation.

RICARDO MARTINEZ, MD
*Stanford, California*

#### REFERENCES

Adult advanced cardiac life support, Pt 3, *In* Standards for Cardiopulmonary Resuscitation (CPR) and Emergency Cardiac Care (ECC). JAMA 1986; 255:2933-2954

Bishop RL, Weisfeldt ML: Sodium bicarbonate administration during cardiac arrest. JAMA 1976 Feb; 235:506-509

Graf H, Leach W, Arieff AI: Evidence for a detrimental effect of bicarbonate therapy in hypoxic lactic acidosis. Science 1985 Feb; 227:754-756

Stacpoole PW: Lactic acidosis: The case against bicarbonate therapy. Ann Intern Med 1986 Aug; 105:276-278

McIntyre KM, Lewis AJ (Eds): Textbook of Advanced Cardiac Life Support. Dallas, American Heart Association, 1983

## Frostbite

FROSTBITE is local injury resulting from freezing cold exposure and remains a serious medical problem. Pathologically, frostbite injuries probably result from a combination of extracellular ice crystal formation with the subsequent development of intracellular osmotic pressure gradient differences that ultimately result in cellular membrane disruption, dehydration and death. Also, microvascular changes including erythrocyte sludging, microthrombous formation and decreased blood flow result in tissue hypoxia and necrosis.

The initial management for deep tissue injury is rapid rewarming in water at 38°C to 41°C (100°F to 106°F). This appears to result in the greatest tissue preservation and has replaced previous folklore such as rubbing the affected part with snow or another body part, exposing to dry heat (such as a campfire) or administering alcohol, as all of these are detrimental. Before rapid rewarming, tissue must be protected to avoid either additional mechanical trauma or freeze-thaw cycles. Refreezing of thawed tissue drastically increases tissue damage and loss. After rapid thawing, adjunctive therapy may include some or all of the following measures: twice-a-day whirlpool baths at temperatures between 32°C and 35°C (90°F and 95°F) containing either povidone-iodine, hexachlorophene or 0.5% silver nitrate; administration of 1% silver sulfadiazine solution to superficially infected open wounds; appropriate management of blisters and blebs—an area of controversy, as some authors advocate leaving blisters intact if uninfected, whereas others recommend debridement and application of thromboxane inhibitors—and giving systemic salicylates concomitantly to inhibit prostaglandin formation. Later, escharotomy may be done on lateral or dorsal aspects of digits after the eschar has dried to increase joint mobility.

Early estimates of tissue damage are difficult, and debridement and amputation are delayed until sufficient time has elapsed (30 to 90 days) for tissues to demarcate and show mummification. Fasciotomy may be required in cases where freezing has been of long duration and where rapid thawing may not restore tissue perfusion. Isotope scanning with the use of sodium pertechnetate Tc 99m or measurement of compartment pressures may all help delineate failure of extremity perfusion and the need for subsequent debridement; other adjunctive measures may include the administration of antibiotics, skin grafting, the use of hyperbaric oxygen, tetanus prophylaxis, sympathectomy, vasodilator therapy, sympathetic blockade, biofeedback and the use of dextran. It is unclear at present whether these therapies improve tissue perfusion enough to affect tissue survival, but it is clear that with the use of some of them, patients will have decreases in pain, edema and infection and will show earlier and more proximal tissue demarcation.

For primary care physicians, the initial management of significant deep cold injury is straightforward, consisting of rapid rewarming. The management thereafter, however, is time-consuming and sometimes confusing because the methods that result in the greatest tissue survival have still not been prospectively delineated.

MICHAEL BARMACHE, MD
*Portland*

#### REFERENCES

McCauley RL, Hing DN, Robson MC, et al: Frostbite injuries: A rational approach based on the pathophysiology. J Trauma 1983; 23:143-147

Mills WJ Jr: Summary of treatment of the cold injured patient—Frostbite. Alaska Med 1983 Apr-Jun; 25:33-38

Salimi Z, Vas W, Tang-Barton P, et al: Assessment of tissue viability in frostbite by $^{99m}$Tc pertechnetate scintigraphy. AJR 1984 Feb; 142:415-419

## Ibuprofen Overdose

IBUPROFEN WAS INTRODUCED as a prescription nonsteroidal anti-inflammatory agent in 1974. It has now been available as an over-the-counter (OTC) medication since 1984, resulting in substantially more widespread use and, hence, a greater probability of overdose and accidental poisoning. Statistics from the American Association of Poison Control Centers indicate a total of 6,510 exposures to ibuprofen in 1985. This compares with a similar exposure rate of 6,425 to OTC aspirin formulations for adults. OTC acetaminophen preparations for adults accounted for 12,100 exposures. Symptoms occurred in 17% of ibuprofen overdoses, compared with aspirin (28%) and acetaminophen (20%). Six deaths were reported from ibuprofen overdose, six from acetaminophen and ten from aspirin overdose. Death rates involving acetaminophen and aspirin are considerably higher if combination narcotic agents are included. Ibuprofen is not currently available in pediatric preparations or in combination with other analgesics.

In a study of ibuprofen overdose, an overall symptomatic rate of 19% was noted, but when children and adults were separated, symptomatic rates were 7% and 47%, respectively, suggesting that the adult overdose, which is usually intentional, is more likely to result in toxic effects.

Mild symptoms of ibuprofen toxicity include abdominal pain, nausea, vomiting, drowsiness, headache, nystagmus and diplopia. Serious toxic effects from overdosage may result in coma, hypotension, bradycardia, apnea, metabolic acidosis and renal failure.

Children ingesting less than 100 mg per kg of ibuprofen

are unlikely to have symptoms and may be observed at home with poison center consultation. Ingestions of 100 to 200 mg per kg may be managed at home with ipecac-induced emesis and observation. If more than 200 mg per kg has been ingested, the child should be referred to an emergency department for evaluation and treatment. All adults should be evaluated and treated because there is a poor correlation between historical data and the incidence of symptoms. Additionally, adults will require emergency psychiatric evaluation following medical treatment.

Treatment is primarily supportive. Airway control and artificial ventilation are indicated depending on a patient's condition. Hypotension is managed with crystalloid and vasopressors, if needed. Seizures should be managed with the administration of diazepam, followed by phenytoin or phenobarbital; the use of sodium bicarbonate may be required for metabolic acidosis. Bradycardia is treated by giving atropine. Ipecac should be administered as soon as possible following ingestion when not contraindicated. Gastric lavage should be done instead of emesis stimulation when a patient is comatose, lethargic or having seizures. Activated charcoal and a cathartic should be administered following completion of gastric emptying. The role for multiple-dose activated charcoal and forced alkaline diuresis as a means to enhance elimination is unproved.

A nomogram has been developed for ibuprofen plasma concentrations similar to that for aspirin and acetaminophen and may be useful in the early prediction of patients who are likely to have symptoms develop. Plasma concentrations are not widely available and are probably not necessary for managing most cases that remain without symptoms for four to six hours. In a series of 126 cases of ibuprofen overdose, symptoms did not develop later than four hours following ingestion.

As ibuprofen becomes more widely available as a nonprescription medication, overdosage will become a more frequent problem requiring treatment in emergency departments.

BRENT T. BURTON, MD
*Portland*

#### REFERENCES

Bennett RR, Dunkelberg JC, Marks ES, et al: Acute oliguric renal failure due to ibuprofen overdose. South Med J 1985 Apr; 78:490-491

Hall AH, Smolinski SC, Conrad FL, et al: Ibuprofen overdose: 126 cases. Ann Emerg Med 1986 Nov 11; 15:1308-1313

Hunt DP, Leigh RJ: Overdose with ibuprofen causing unconsciousness and hypotension. Br Med J 1980; 281:1458-1459

Litovitz TL, Norman SA, Veltri JC: 1985 Annual report of the American Association of Poison Control Centers national data collection system. Am J Emerg Med 1986 Sep; 4:427-458

## Transcutaneous Cardiac Pacing

TRANSCUTANEOUS CARDIAC PACING was initially described in 1952, but its use was generally abandoned because of the painful muscle contraction and interference with electronic monitoring associated with its use and the development of other techniques of cardiac pacing. Recently interest has been renewed because of the recognized need for an effective, noninvasive, rapidly initiated method of cardiac pacing.

The procedure is relatively simple and requires little training. An external pacing device is connected to two large electrodes. These electrodes are about 8 cm in diameter and are placed in an anterior (cardiac apex)-posterior (left subscapular) configuration. Successful pacing, if it is going to occur, generally requires about 50 to 100 mA. The pacing device can be used in either the demand or fixed-rate mode depending on the clinical circumstances. Electrical capture rates and resulting hemodynamic improvement appear to be equal to transvenous pacing over short periods of time.

Both patients with asystole and those with bradycardia with hemodynamic dysfunction may benefit from the use of transcutaneous pacing. In patients with cardiac arrest the success rate of electrical capture and hemodynamic improvement has been low, but in those with heart block or bradycardia with some perfusion, the results of pacing have been much better. The adoption of larger electrodes that decrease skin stimulation and longer pacing stimuli that decrease the electrical threshold for capture has enabled most awake patients to tolerate the procedure. Ventricular arrhythmias have not been initiated and damage to the myocardium has not occurred with the use of this technique.

Transcutaneous pacing is a rapid and effective method of pacing the heart in emergency situations. It should be considered for use in asystolic patients and those with bradycardia and hemodynamic dysfunction.

KENNETH J. RHEE, MD
*Sacramento, California*

#### REFERENCES

Clinton JE, Zoll PM, Zoll RH, et al: Emergency noninvasive external cardiac pacing. J Emerg Med 1985; 2:155-162

Dalsey WC, Syverud SA, Hedges JR: Emergency department use of transcutaneous pacing for cardiac arrests. Crit Care Med 1985 May; 13:399-401

Falk RH, Zoll PM, Zoll RH: Safety and efficacy of noninvasive cardiac pacing—A preliminary report. N Engl J Med 1983 Nov; 309:1166-1168

Paris PM, Stewart RD, Kaplan RM: Transcutaneous pacing for bradyasystolic cardiac arrests in prehospital care. Ann Emerg Med 1985; 14:320-323

## Evaluating Patients With Tricyclic Antidepressant Overdose for Risk of Complications

PATIENTS WHO INGEST tricyclic antidepressant drugs present multiple problems for emergency physicians. Over the years, a relatively standardized treatment of major toxic reactions has developed that includes supportive care, systemic alkalinization and selected antiarrhythmics. In-hospital cardiac monitoring for all patients with evidence of possible tricyclic antidepressant overdose has also become common practice. There has long been concern over whether the use of monitored beds is warranted for patients who present with minimal findings. The isolated reports of serious "delayed" toxic reactions after initially having near-normal findings were taken as evidence, however, that an emergency physician had no choice but to seek admission and monitoring for almost all patients, no matter how apparently trivial their poisoning on initial presentation.

A stumbling block in this dilemma has been the lack of a simple reliable indicator for toxicity. Measuring serum drug concentrations has been shown to be unreliable. The QRS interval on an electrocardiogram was shown in early work to have some correlation with toxic effects but not to be highly accurate or predictive. Recently in a small prospective study, the QRS interval was reported to be an accurate indicator for a risk of ventricular arrhythmias or seizures, but a retrospective review by other authors failed to confirm this. Further prospective studies are needed on this issue.

While an ideal indicator of toxicity risk has not been identified, observing patients for the presence or absence of certain clinical signs may identify those patients at minimal or no risk of a subsequent toxic condition. As early as 1981, a

clinical study reported that all patients who died displayed manifestations of a toxic reaction early in their clinical course. A recent review of the rare cases of "delayed toxicity" showed they occurred in patients who did not receive the modern standard of gastric emptying and activated charcoal administration. A large-scale epidemiologic review of fatalities due to tricyclic antidepressant overdose has shown that all patients who arrive at a hospital alive will manifest significant signs of toxic effects within an hour of presentation. Other clinical studies of patients admitted with nonfatal tricyclic antidepressant overdosage have confirmed this finding that significant evidence of a toxic reaction occurs during the early hours of evaluation, if it is to occur at all.

Multiple studies now indicate that initially observing patients who present with possible tricyclic antidepressant overdosage for a period of six hours should identify a group with a low risk of a subsequent serious toxic reaction. All patients should have their stomachs emptied, receive activated charcoal and have electrocardiographic monitoring. A patient who has altered consciousness, arrhythmias, seizures, respiratory compromise, cardiac conduction defects or hypotension warrants intensive care admission. Other patients can be relegated to a lower level of medical or psychiatric (depending on condition) care. Patients who show no toxic effects other than sinus tachycardia after appropriate initial decontamination and six hours of careful observation are in an extremely low-risk group and may be suitable for outpatient management after psychiatric evaluation.

GARRETT E. FOULKE, MD
*Sacramento, California*
MICHAEL CALLAHAM, MD
*San Francisco*

#### REFERENCES

Boehnert MT, Lovejoy FH Jr: Value of the QRS duration versus the serum drug level in predicting seizures and ventricular arrhythmias after an acute overdose of tricyclic antidepressants. N Engl J Med 1985 Aug; 313:474-479

Callaham M, Kassel D: Epidemiology of fatal tricyclic antidepressant ingestion: Implications for management. Ann Emerg Med 1985 Jan; 14:1-9

Foulke GE, Albertson TE: QRS interval in tricyclic antidepressants overdosage: Inaccuracy as a toxicity indicator in emergency settings. Ann Emerg Med 1987 Feb; 16:160-163

Foulke GE, Albertson TE, Walby WF, et al: Tricyclic antidepressant overdose: Emergency department findings as predictors of clinical course. Am J Emerg Med 1986; 4:496-500

Stern TA, O'Gara PT, Mulley AG, et al: Complications after overdose with tricyclic antidepressants. Crit Care Med 1985 Aug; 13:672-674

## Treatment of Snakebite

RATTLESNAKE BITES should be considered a medical emergency, and patients should be quickly transported to a hospital. The clinical findings following snake envenomation are dependent on many variables. The toxicity of venom varies among the 25 or more species of rattlesnakes in the United States. In about 15% to 25% of the victims bitten by vipers, no envenomation occurs. If a victim is bitten and envenomated, the amount of venom injected depends on many factors such as the activity of the snake, defensive or offensive posturing, the size of the snake and the depth and number of bites.

Recommendations for the treatment of rattlesnake bites have been the subject of debate. Tourniquets may not be helpful in affecting overall outcome. Originally designed to obstruct lymph flow, the significance of lymph drainage to systemic morbidity and mortality has never been clearly established. In addition, tourniquets may be applied too tightly, leading to venous congestion and further damage to an already injured extremity. In general, incision and suction may not be helpful in the field management of most snakebites and may only add insult to injury. Some authorities still recommend suction if a patient is more than an hour away from definitive care, but it must be begun within 5 minutes and is of absolutely no use if started more than 15 minutes after envenomation. At best no more than 10% to 20% of the venom can be removed. In the past, applying ice had been recommended to cool the snakebite area locally or even an entire extremity. This is no longer recommended.

Recently the American Association of Poison Control Centers and the American College of Emergency Physicians have recommended the following measures for first aid: "(1) immobilize the bitten part, (2) remove constrictive items and rings, (3) put the victim at rest and (4) transport to the nearest medical facility."

Numerous measures should be begun immediately when a patient arrives at hospital. Laboratory studies such as a complete blood count, electrolyte levels, arterial blood gas determinations, fibrinogen titers, urinalysis, platelet count, clotting times, prothrombin and partial thromboplastin times and type and crossmatch should be done immediately. Antivenom available in the United States for the treatment of rattlesnakes is a polyvalent blend effective against all species. Its use should be considered in all patients with systemic signs of envenomation and those with significant local effects. Rattlesnake bites are generally classified as minimal, moderate or severe. The guidelines for the use of antivenom are as follows: minimal bites, 5 to 8 vials; moderate bites, 8 to 12 vials, and severe bites, 13 vials or more as titrated to clinical condition. The patient should be skin tested before administering the antivenom, as it is derived from horse serum. If a patient is allergic to the antivenom, it can be given cautiously in conjunction with other measures described elsewhere. As many as ten ampules can be placed in 500 ml of a normal saline solution and run in over a one-hour period. Recent recommendations have discouraged the use of corticosteroids (except in patients hypersensitive to antivenom) and excisional therapy. A fasciotomy for compartment syndromes should only be considered when objective monitoring shows elevated pressures unresponsive to antivenom.

ROBERT W. DERLET, MD
GARRETT E. FOULKE, MD
*Sacramento, California*

#### REFERENCES

Arizona Poison and Drug Information Center: Snake Venom Poisoning Chart. Tucson, Arizona Health Sciences Center, University of Arizona, August 1984

Butner AN: Rattlesnake bites in northern California. West J Med 1983 Aug; 139:179-183

Hardy DL, Kunkel DB, Russell FE, et al: Management of poisonous snakebite. J Vet Hum Toxicol 1983 Apr; 25:135-137

Russell FE: Snake venom poisoning in the United States. Annu Rev Med 1980; 31:247-259

## Clinical Uses for a New β-Lactamase Inhibitor Antibiotic

AMPICILLIN and its analog, amoxicillin, have been considered the initial drugs of choice for treating bacterial infections involving the genitourinary tract, respiratory tract, sinuses and middle ear. Recently, however, common bacterial respiratory pathogens such as *Hemophilus influenzae* and genitourinary pathogens such as *Escherichia coli, Proteus mirabilis* and *Neisseria gonorrhoeae* have become increasingly resistant. *Staphylococcus aureus* has long been resistant to penicillins. In addition, newly recognized respiratory pathogens

such as *Branhamella catarrhalis, Legionella* species and anaerobes such as *Bacteroides fragilis* display penicillin resistance. The emergence of bacteriologic resistance has coincided with increasing clinical failures.

The basis for this resistance is bacterial production of β-lactamase, an enzyme that renders the penicillin inactive. Recently an oral antibiotic has been introduced in which a β-lactamase inhibitor, clavulanate, is combined with amoxicillin (Augmentin). Clavulanate protects the amoxicillin from destruction by β-lactamases of many organisms including all those mentioned above. Over the past five years, studies have shown the effectiveness of Augmentin in treating many adult and pediatric infections.

Augmentin has been shown to be effective for the treatment of acute otitis media and trials have shown it to be equal or superior to cefaclor. It has been recommended for patients who do not initially respond to first-line drugs or for initial therapy in areas where the incidence of β-lactamase-producing bacteria is high. Augmentin has also been shown to be effective for treating acute sinusitis, bronchitis and pneumonia. Recent in vitro studies suggest that *Legionella* species are sensitive to Augmentin.

The incidence of β-lactam-resistant urinary tract infections has steadily increased. Augmentin has been shown to be effective in treating resistant infections. It is currently being evaluated as a single-dose therapy for uncomplicated urinary tract infections.

Penicillinase-producing *N gonorrhoeae* now constitutes a serious health problem. Augmentin is highly active in vitro for these organisms and its use is currently being evaluated clinically.

Augmentin has been shown to successfully treat skin and soft tissue infections. It is an ideal single drug to treat animal bites, as it covers the most common pathogens, *S aureus* and *Pasteurella multocida*.

This combination drug represents a significant addition to the antibiotic armamentarium of emergency physicians.

DAVID A. TALAN, MD
*Sylmar, California*

**REFERENCES**

Amoxicillin-clavulanic acid (Augmentin). Med Lett Drugs Ther 1984 Nov; 26:99-100

Goldstein EJC, Reinhardt JR, Murray PM, et al: Animal and human bite wounds: A comparative study, Augmentin vs penicillin +/- dicloxacillin, *In* Progress and Perspectives on β-Lactamase Inhibitors: A Review of Augmentin. Postgrad Med 1984 Sep-Oct; (a special report):105-110

Marchant CD, Shurin PA, Johnson CE, et al: A randomized controlled trial of amoxicillin plus clavulanate compared with cefaclor for treatment of acute otitis media. J Pediatr 1986 Nov; 109:891-896

Tolkoff-Rubin NE, Rubin RH, Weber DJ: Augmentin in the treatment of urinary tract infection, *In* Progress and Perspectives on β-Lactamase Inhibitors: A Review of Augmentin. Postgrad Med 1984 Sep-Oct; (a special report):78-85

## Cephalosporins for Bacterial Meningitis

THIRD-GENERATION CEPHALOSPORIN antibiotics have been used successfully in the treatment of acute bacterial meningitis. These agents are now preferred for the treatment of Gram-negative bacillary meningitis and for the empiric therapy for bacterial meningitis in immunocompromised or high-risk patients. They are often chosen by pediatricians in the empiric treatment of bacterial meningitis in patients from the newborn period through childhood.

The experience with the use of first-generation cephalosporins in bacterial meningitis was disappointing because of the low concentrations of these antibiotics in the cerebrospinal fluid (CSF). Of the second-generation cephalosporins, including cefamandole, cefoxitin and cefuroxime, only cefuroxime has proved efficacious in treating meningitis caused by *Neisseria meningitidis, Diplococcus pneumoniae* or *Hemophilus influenzae*. The third-generation cephalosporins offer new advantages in the treatment of meningitis because they are active at obtainable CSF concentrations, the bacteria that cause most cases of meningitis are not resistant and the drugs are safer than many of the standard antibiotics recommended for meningitis—that is, chloramphenicol and aminoglycosides.

The organisms most often responsible for neonatal meningitis are group B streptococcus and *Escherichia coli*. Thus, ampicillin and gentamicin sulfate are the standard antibiotics chosen for the empiric treatment of neonatal meningitis pending CSF and blood culture results. But recent studies have shown that using a combination of ampicillin (to cover the possibility of *Listeria*) and one of several third-generation cephalosporins (cefotaxime sodium, ceftriaxone sodium or cefuroxime) is equally efficacious. This regimen also avoids the necessity to follow serum or CSF (or both) gentamicin concentrations and to administer aminoglycosides intrathecally.

After the first two months of life and during the remainder of the first decade of life, *H influenzae* type B, *D pneumoniae* and *N meningitidis* are the organisms responsible for most cases of meningitis. The standard recommendation for empiric antibiotic therapy pending CSF culture results is to give ampicillin and chloramphenicol. The distinction, however, between the different types of bacteria causing meningitis based on whether a patient is younger or older than 2 months of age is becoming less reliable. Furthermore, ampicillin resistance due to the production of β-lactamase by *Hemophilus* is a common problem now, and chloramphenicol resistance due to acetyltransferase production by *Hemophilus* is predicted to become a common problem within a few years. Finally, it is recommended that chloramphenicol concentrations be monitored to avoid subtherapeutic or toxic concentrations in younger patients. Thus, third-generation cephalosporins (such as cefotaxime, ceftriaxone and cefuroxime) have again been found efficacious both in treating meningitis due to *H influenzae* and in avoiding the many problems associated with the standard therapies.

In adolescents and in adults, penicillin is the antibiotic of choice because bacterial meningitis in these age groups is usually due to either *D pneumoniae* or *N meningitidis*. There are, however, some strains (between 3% and 16%) of pneumococci that are relatively resistant to penicillin and ampicillin, necessitating greater dosages to sterilize the CSF. Furthermore, *Hemophilus* is causing more cases of meningitis in these older age groups, which necessitates the use of antibiotics other than penicillin. And as the number of high-risk patients—such as those who are immunocompromised, alcoholic, elderly, have had a neurosurgical procedure and so forth—increases, so does the number of cases of meningitis due to *Listeria* (ampicillin is recommended) or Gram-negative organisms. The third-generation cephalosporin antibiotics—that is, cefotaxime, ceftriaxone and moxalactam—are very active against Gram-negative bacilli and they reach significant CSF concentrations. Thus, these newer cephalosporins are the agents of choice for the treatment of Gram-negative bacillary meningitis.

Caution is necessary to properly treat bacterial meningitis

with the third-generation cephalosporins. First, for the treatment of pneumococcal or meningococcal meningitis, penicillin or chloramphenicol remain the recommended antibiotics. Second, other Gram-positive cocci, in particular *Staphylococcus aureus*, are resistant to the newer cephalosporins. Third, the use of chloramphenicol apparently interferes with the activity of cefotaxime, which led to treatment failure in a patient with meningitis due to *Klebsiella*. Chloramphenicol may similarly interact with other third-generation cephalosporins. Fourth, not all Gram-negative species and not all organisms of any particular species are sensitive to these agents. For example, there are case reports of *E coli* resistance to moxalactam. And most *Pseudomonas* strains are resistant, as are all *Acinetobacter*, enterobacter and enterococci. Finally, as mentioned previously, *Listeria* infections should be treated with ampicillin.

GARY P. YOUNG, MD
*Oakland, California*

#### REFERENCES

Beam TR Jr: Cephalosporins in adult meningitis. Bull NY Acad Med 1984 May; 60:380-393

Bolan G, Barza M: Acute bacterial meningitis in children and adults—A perspective. Med Clin North Am 1985 Mar; 69:231-241

Klein JO, Feigin RD, McCracken GH Jr: Report of the task force on diagnosis and management of meningitis. Pediatrics 1986; 78:959-982

Nelson JD: Emerging role of cephalosporins in bacterial meningitis. Am J Med 1985 Aug; 79:47-51

## Indications for Hyperbaric Oxygen Therapy

HYPERBARIC OXYGEN THERAPY, whereby a patient breathes 100% oxygen at an atmospheric pressure greater than sea level, has been the mainstay in the treatment of decompression sickness and gas emboli in divers. It is also an emerging treatment for a number of other medical indications.

The Hyperbaric Oxygen Therapy Committee of the Undersea and Hyperbaric Medical Society has classified the uses of hyperbaric oxygen into "accepted" and "investigative" indications, with a "special category" for clinically controversial indications. Accepted indications are listed in the table, while the list of investigative indications can be found in the committee's report. For some conditions, such as prophylaxis for osteoradionecrosis, the use of hyperbaric oxygen is primary therapy, while for other indications it is adjunctive to other interventions, such as for chronic refractory osteomyelitis, where antibiotics and definitive surgical therapy must also be used. The adjunctive use of hyperbaric oxygen for thermal injuries remains controversial.

TABLE 1.—*Accepted Indications for Use of Hyperbaric Oxygen*

| |
|---|
| Acute air or gas embolism |
| Carbon monoxide or cyanide poisoning |
| Crush injuries and compartment syndromes |
| Decompression sickness |
| Enhancement of healing in selected problem wounds, particularly in some diabetic wounds |
| Exceptional blood loss anemia |
| Clostridial gas gangrene |
| Necrotizing soft tissue infections, such as crepitant anaerobic cellulitis, progressive bacterial gangrene, necrotizing fasciitis, nonclostridial myonecrosis and Fournier's gangrene |
| Chronic refractory osteomyelitis |
| Radiation necrosis of bone or soft tissue |
| Dental extraction from irradiated bone |
| Nonhealing of skin grafts or flaps |
| Actinomycosis |

Newly established has been the ability of hyperbaric oxygen to statistically significantly reduce the development of osteoradionecrosis after tooth removal from previously irradiated jaws. There has been a reduction from 29.9% to only 5.4% in the development of the disorder when hyperbaric oxygen was used before and after the extraction, compared with a penicillin-treated study group. Extraordinary cost-savings were also shown.

Additional recent developments in the field are the demonstration of the effectiveness of hyperbaric oxygen for treating radiation-induced hemorrhagic cystitis and a new classification and staging system for osteomyelitis, to facilitate further study uniformity and allow the proper selection of patients for therapy.

Case selection is important in most of the listed categories, and early consultation with a physician experienced in the treatment of patients with hyperbaric oxygen should be sought.

IRVING JACOBY, MD
*San Diego*

#### REFERENCES

Cierny G III, Mader JT, Penninck JJ: A clinical staging system for adult osteomyelitis. Contemp Orthopaedics 1985 May; 10:17-37

Hyperbaric Oxygen Therapy: A Committee Report, publication No. 30CR (HBO). Bethesda, Md, Undersea and Hyperbaric Medical Society, 1986

Marx RE, Johnson RP, Kline SN: Prevention of osteoradionecrosis: A randomized prospective clinical trial of hyperbaric oxygen versus penicillin. J Am Dent Assoc 1985; 111:49-54

Weiss JP, Boland FP, Mori H, et al: Treatment of radiation-induced cystitis with hyperbaric oxygen. J Urol 1985 Aug; 134:352-354

## Cardiopulmonary Resuscitation and Defibrillation

EVERY FIVE OR SIX YEARS the American Heart Association convenes a national conference to revise and update the standards for cardiopulmonary resuscitation (CPR) and advanced cardiac life support. Such a meeting (the third since 1973) was held July 1985 in Dallas, and the standards and guidelines were published in *The Journal of the American Medical Association*. (A complete copy of the "Standards and Guidelines for Cardiopulmonary Resuscitation [CPR] and Emergency Cardiac Care [ECC]" may be obtained from local chapters of the American Heart Association.)

The new standards for CPR simplify the technique. First, one-person CPR will be emphasized for layperson CPR instruction. Second, ventilations will no longer be "stacked" but rather given as two sequential breaths over two to three seconds (1 to 1½ seconds per breath), and the use of four initial breaths has been dropped with two breaths being used throughout. Third, the rate of chest compressions has been increased to a rate of 80 to 100 per minute. The ratio of 15 compressions to 2 ventilations is maintained. For two-person CPR there should be a pause in chest compressions while ventilation occurs. The ratio of five compressions to one ventilation is maintained.

The new guidelines for advanced cardiac life support emphasize the importance of rapid defibrillation for ventricular fibrillation. For ventricular fibrillation the sequence consists of a 200-J defibrillatory shock, and if ventricular fibrillation persists, a second shock of 200 to 300 J and, if necessary, a third shock of as much as 360 J. Only then, if fibrillation persists, should pharmacologic therapy begin with the use of epinephrine and antiarrhythmics. Defibrillation, assuming a

defibrillator is present, takes precedence over intubation, intravenous line placement and even CPR. The use of sodium bicarbonate is deemphasized and is merely considered rather than recommended well into the resuscitation. For asystole and electromechanical dissociation, the use of calcium has been eliminated.

MICKEY EISENBERG, MD
*Seattle*

#### REFERENCES

Standards and Guidelines for Cardiopulmonary Resuscitation (CPR) and Emergency Cardiac Care (ECC). JAMA 1986; 255:2905-2989

Weisfeldt ML, Halperin HR: Cardiopulmonary resuscitation: Beyond cardiac massage. Circulation 1986 Sep; 74:443-448

## Expanding the Use of Automatic External Defibrillators to Home and Community

THE SINGLE most effective intervention in cardiac arrest occurring outside the hospital is early external defibrillation. The problem is that ventricular fibrillation is a very transient rhythm, lasting only a few minutes before it decays to asystole, from which virtually no one can be resuscitated. A major thrust in emergency medicine has been to develop ways to get a defibrillator to a patient in cardiac arrest as quickly as possible. Paramedics in mobile coronary care units were, in their original conception, "invented" so that they could carry defibrillators to such patients. Next, emergency medical technicians (EMTs), less well trained than paramedics but more than ten times as plentiful, were trained to identify ventricular fibrillation and to deliver a defibrillatory shock when they discovered a patient in that rhythm. The problem still remains, however, that emergency personnel can take a long time to get a defibrillator to a patient's side.

The rationale behind early defibrillation strongly suggests that the immediate witnesses of an arrest, bystanders, family members and colleagues at work should also be given defibrillators. Unfortunately, interpreting cardiac rhythms and operating a sophisticated medical device are beyond the ability of most laypersons and even some less-experienced emergency personnel.

Since the late 1970s several companies have worked to develop portable battery-powered defibrillators that could automatically analyze a patient's cardiac rhythm for the presence of ventricular fibrillation. If fibrillation occurs, the devices, called automatic external defibrillators, charge their capacitors and deliver an electrical countershock.

At this time, these defibrillators are being evaluated in several settings. Researchers have studied their use in the homes of patients who have survived either a cardiac arrest or a myocardial infarction. Their work has confirmed that family members of a high-risk patient can be successfully trained to operate an automatic external defibrillator, that they can retain this knowledge over long periods of time and that they will successfully use the device when an actual cardiac arrest occurs.

Fully trained paramedics can diagnose dysrhythmias, insert intravenous lines, administer medication and carry out defibrillation. While lesser-trained EMTs generally lack these skills, they are much more numerous than paramedics and can usually reach a patient more rapidly. The use of automatic external defibrillators by EMTs may partially compensate for their lesser amount of training because rhythm recognition is done by the device, rather than by emergency personnel. Two large controlled trials have confirmed the value of their use by EMTs.

Placing automatic external defibrillators in public settings is another strategy to achieve rapid defibrillation after a cardiac arrest. Researchers are currently conducting evaluations of such placement in senior centers, community health clubs, high-rise office buildings and large corporate settings.

Methods to deal with medical emergencies in the air have remained controversial and hotly debated. One major airline has embarked on a two-year evaluation of the use of automatic defibrillators by trained cabin-crew members in wide-body aircraft that fly international routes.

During the next decade, automatic defibrillators will become smaller, less expensive, safer and more accurate. They are clearly a device of the future.

RICHARD O. CUMMINS, MD
*Seattle*

#### REFERENCES

Cummins RO, Eisenberg MS, Litwin PE, et al: Automatic external defibrillators used by emergency medical technicians: A controlled clinical trial. JAMA 1987; 257:1605-1610

Cummins RO, Eisenberg MS, Hearne TR, et al: Community responder use of automatic external defibrillators: Ease of training and retention of skills (Abstr). Am J Emerg Med 1986; 4:417

Moore JE, Eisenberg MS, Andresen E, et al: Home placement of automatic external defibrillators among survivors of ventricular fibrillation. Ann Emerg Med 1986; 15:811-812

Stults KR, Brown DD, Kerber RE: Efficacy of an automated external defibrillator in the management of out-of-hospital cardiac arrest: Validation of the diagnostic algorithm and initial clinical experience in a rural environment. Circulation 1986; 73:701-709

Weaver WD, Copass MK, Hill D, et al: Development and widespread use of automatic external defibrillators (Abstr). Am J Emerg Med 1986; 4:424-425

## Advances in Radiologic Evaluation of Acute Spinal Cord Compression

ACUTE SPINAL CORD compression in cancer patients is a true oncologic emergency. Without prompt intervention, potentially reversible neurologic damage will become permanent. Although direct parenchymal metastatic invasion of the spinal cord is rare, most cancer patients with cord compression present with spinal epidural metastases from the direct spread of vertebral or paravertebral lesions.

While neurologic examination and plain radiographs help to localize the level of the lesion, myelography, using either iophendylate (oil-based), metrizamide (water-soluble) or both as contrast, has been the standard radiologic examination. By using sagittal projection, several levels of obstruction can be visualized simultaneously and spot radiography limits motion artifact. The procedure is invasive, however, often requiring two punctures above and below the lesion to define the extent of obstruction. As only the outline of the soft tissue is visualized, the actual extent of a paravertebral lesion cannot be seen.

The development of high-resolution computed tomography (CT) allows for greater distinction between bone and soft tissue. The transverse view of the spine provides visualization of the perispinal area, allowing a view not only of impingement of the cord but also the extent of epidural metastases. The procedure is noninvasive and requires no contrast material, but within the confines of the spinal canal there is poor resolution between the cord and the subarachnoid space.

A solution to this problem is the use of water-soluble metrizamide contrast with computer-assisted myelography. This improves differentiation between the soft tissues, and transverse views better show the extent of cord compression than does myelography. As smaller amounts of metrizamide

are detected by CT, what appears to be a complete block on routine myelography is often shown to be incomplete with computer-assisted myelography, thus obviating the need of a second puncture above the lesion. This greater sensitivity also allows for the use of smaller doses of metrizamide, particularly important in evaluating upper cord lesions that have the added risk of seizures due to contrast material.

Still, the use of computer-assisted myelography is not without its disadvantages. The procedure is invasive, requires contrast, exposes a patient to radiation and is limited to transverse projection.

Although in its relative infancy, magnetic resonance imaging (MRI) provides a new and in many ways superior evaluation of cord compression. The spine can be seen in both the sagittal and transverse projections. Abnormalities in cord diameter and contour are easily seen. Differences in soft-tissue densities are better delineated. As such, MRI is as accurate as CT and myelography in showing the cranial and caudal levels of obstruction without the invasive use of contrast material or exposure to radiation.

MRI, however, is not without its limitations. Slice thickness, although improving, is still quite large compared with CT. The procedure is relatively lengthy, and patient handling is more difficult in the confined spaces of MRI. Patients requiring advanced life-support equipment or cardiac pacemakers cannot be studied. Nevertheless, as technologic advances correct these limitations, MRI shows great potential as the diagnostic tool of choice in the evaluation of spinal cord compression.

ROBERT L. GALLI, MD
*Sylmar, California*

#### REFERENCES

Barrow DL, Wood JH, Hoffman JC Jr: Clinical indications for computer-assisted myelography. Neurosurgery 1983 Jan; 12:47-57

Paushter DM, Modic MT, Masaryk TJ: Magnetic resonance imaging of the spine: Applications and limitations. Radiol Clin North Am 1985 Sep; 23:551-562

Wang AM, Lewis ML, Rumbaugh CL, et al: Spinal cord or nerve root compression in patients with malignant disease: CT evaluations. J Comput Assist Tomogr 1984 Jun; 8:420-428

## Computed Tomography Versus Peritoneal Lavage in Blunt Abdominal Trauma

PERITONEAL LAVAGE has for years been a useful technique in the evaluation of blunt abdominal trauma. Recently, however, computed tomography (CT) has gained favor and in many institutions has replaced lavage as the most frequently used modality.

Three questions are crucial to the evaluation of blunt abdominal trauma: (1) is blood present? (2) how much blood is present? (3) what organs are damaged? Tomography is superior to lavage in answering questions 2 and 3 and has some advantages relative to question 1.

*Is blood present?* Lavage is very sensitive in diagnosing intraperitoneal blood. Many studies have indicated that CT is equally sensitive, although some recent articles discussed below have questioned its reliability. There is no question, however, that lavage does not detect retroperitoneal hemorrhage, whereas CT does. Moreover, unlike CT, lavage may yield false-positive results due to either a traumatic tap or dissection of retroperitoneal blood into the peritoneal cavity through torn fascial planes.

*How much blood is present?* While lavage may detect intraperitoneal bleeding, it may not be very accurate in measuring the amount of free blood. Many clinically stable patients who might undergo laparotomy based on abnormalities detected by lavage can avoid surgical intervention if intraperitoneal bleeding is estimated to be relatively minor based on CT findings. In two studies, 60% of patients with liver lacerations and 79% of children with splenic injury were spared laparotomy.

*What organs are damaged?* Lavage offers no information regarding the specific organ(s) damaged. CT is quite sensitive and specific for the most frequently injured organs: liver, spleen and kidney. It is less sensitive for bowel and pancreatic trauma, but can often detect injuries to these organs as well.

Tomography does require time and is indicated only for patients who are hemodynamically stable. Unstable patients with obvious abdominal injuries should be taken directly to the operating room. Results of a previous lavage may be useful in confirming free intraperitoneal bleeding in such patients if there is any question.

While a number of studies have indicated nearly 100% sensitivity of CT in detecting clinically significant intraperitoneal bleeding, several recent articles have reported dramatically less sensitivity. The discrepancy between results from reputable trauma centers is disturbing and indicates that the issue has not yet been resolved. It is suggested that relying on CT alone in institutions with relatively little experience is not advisable. Yet the reports from some major trauma centers suggest that in hospitals with sufficient volume, CT may prove to be the most useful method for evaluating blunt abdominal trauma. Even one of the articles casting doubt on the reliability of CT states that if experienced CT interpretation is immediately available to determine the need for laparotomy, CT may be equal in sensitivity to lavage. Regardless of how the issue is ultimately resolved, however, there is no question that peritoneal lavage will always have an important role.

MICHAEL J. BRESLER, MD
*Stanford, California*

#### REFERENCES

Fabian TC, Mangiante EC, White TJ, et al: A prospective study of 91 patients undergoing both computed tomography and peritoneal lavage following blunt abdominal trauma. J Trauma 1986 Jul; 26:602-608

Federle MP: Computed tomography of blunt abdominal trauma. Radiol Clin North Am 1983 Sep; 21:461-475

Goldstein AS, Sclafani SJA, Kupferstein NH, et al: The diagnostic superiority of computerized tomography. J Trauma 1985 Oct; 25:938-946

Marx JA, Moore EE, Jorden RC, et al: Limitations of computed tomography in the evaluation of acute abdominal trauma: A prospective comparison with diagnostic peritoneal lavage. J Trauma 1985 Oct; 25:933-937

Peitzman AB, Makaroun MS, Slasky BS, et al: Prospective study of computed tomography in initial management of blunt abdominal trauma. J Trauma 1986 Jul; 26:585-592

## Digoxin-Specific Fab Fragments

THE DEVELOPMENT of digoxin-specific antibodies has provided a significant therapeutic option for the treatment of digitalis intoxication. Hitherto experimental and available only at a limited number of centers, digoxin-immune Fab (Digibind) has been commercially released within the past year. The antibodies are produced by immunizing animals with digoxin coupled to a protein carrier, removal of serum, enzymatic digestion of the immune complex and separation of the digoxin-specific Fab fragments. Administered intravenously, the fragments bind to digoxin, rendering it pharmacologically inactive.

Fab fragments should be administered to a patient with digoxin or digitoxin intoxication who exhibits serious cardiac rhythm disturbance, hyperkalemia or both. Mild to pro-

nounced hyperkalemia is typically present in acute digitalis intoxication. The standard management of acute drug ingestion and antidysrhythmic management should be initiated until the immune fragments can be given. Therapy is considered successful if the rhythm disturbances cease and hyperkalemia resolves. Clinical trials have described remarkable success with the use of antibody fragments, with reversal of toxicity usually occurring within minutes to hours.

No notable side effects, adverse effects or hypersensitivity reactions have been reported following administration of Fab fragments. There is, however, limited experience with reexposure of patients to these agents. In patients with adequate renal function, the digoxin-Fab complex is fairly rapidly eliminated by glomerular filtration, with a half-life of about 16 to 20 hours. Once antibody fragments are administered, serum digoxin determinations become invalid as indicators of a patient's course because inactive, antibody-bound digoxin is measured.

The contents of a single vial of antibody fragments will bind approximately 0.6 mg of digoxin. The amounts required in treatment will vary with the quantity of digitalis ingested. An average of 12.5 vials per patient has been used in several major series. It has been recommended that 25 vials be stored at the treatment center.

GEORGE STERNBACH, MD
*Stanford, California*

**REFERENCES**

Cole PJ, Smith TW: Use of digoxin-specific Fab fragments in the treatment of digitalis intoxication. Drug Intell Clin Pharm 1986 Apr; 20:267-270

Wenger TL, Butler VP Jr, Haber E, et al: Treatment of 63 severely digitalis-toxic patients with digoxin-specific antibody fragments. J Am Coll Cardiol 1985; 5(suppl A):118-123A

Zalcberg JR: Monoclonal antibodies to drugs: Novel diagnostic and therapeutic reagents. Pharmacol Ther 1985; 28:273-285

## ADVISORY PANEL TO THE SECTION ON EMERGENCY MEDICINE

DANIEL D. WHITCRAFT, MD
*Advisory Panel Chair*
*CMA Scientific Board Representative*
*Long Beach*

ELLEN TALIAFERRO, MD
*CMA Section Chair*
*Bakersfield*

MARK C. SMEDLEY, MD
*CMA Section Secretary*
*Sacramento*

STEPHEN J. GROTH, MD
*CMA Section Assistant Secretary*
*Huntington Beach*

DONALD MINESINGER, MD
*Loma Linda University*

MICHAEL ELIASTAM, MD
*Stanford University*

ROBERT W. DERLET, MD
*University of California,Davis*

KYM SALNESS, MD
*University of California,Irvine*

JEROME HOFFMAN, MD
*University of California,Los Angeles*

IRVING JACOBY, MD
*University of California,San Diego*

FRANK LEWIS, MD
*University of California,San Francisco*

GAIL ANDERSON, MD
*University of Southern California*

LARRY BEDARD, MD
*Sausalito*

RICHARD GILLESPIE, MD
*Santa Rosa*

MICHAEL J. BRESLER, MD
*Section Editor*
*Stanford University*

WILLIAM J. KOENIG, MD
*Long Beach*

# Editorials

## Whatever Happened to Report MM?

AT ITS MEETING in June 1986 the House of Delegates of the American Medical Association (AMA) adopted Report MM of the Board of Trustees, entitled "Proposal for Financing Health Care of the Elderly." This report was developed as a result of careful study by the AMA Councils on Medical Service and Legislation. It did not purport to be the final word but was rather presented as a springboard for wider discussion. But, to this writer's knowledge, there has so far been little, if any, wider discussion.

It is to be hoped that this thoughtful and far-sighted proposal is not destined simply to gather dust on some shelf where no one is likely to be either stimulated or disturbed by it. The financing of health care for the elderly is already in serious jeopardy for the long term. The problem is not likely to go away. Rather it will soon be upon us, since the number and proportion of elderly persons in our society increases substantially every year. But reports and studies such as this proposal are not likely to become widely known or widely discussed without some affirmative promotion, or even some aggressive marketing, by its sponsors. It is the way of good and important reports to become ignored unless someone does something to counteract the inertia with which any proposals for fundamental change are always met. The weight of this very real inertia tends either to push a novel idea aside or, more often, to bury it.

Report MM of the June 1986 House of Delegates is an important insight into what needs to be done about financing health care for the elderly. It should not be shelved or buried. It should be given aggressive exposure by its sponsors, the physicians of the nation, who are concerned and informed about health care of the elderly, and that it be financed appropriately.

MSMW

## The Surgeon's Approach to Hypoglycemia in Infants and Children

IN THIS ISSUE, Moossa and co-workers review hypoglycemic syndromes in infancy and childhood and present a surgeon's perspective on the treatment. In addition, they draw upon experience over a 13-year period with five infants treated with 90% pancreatectomy, although no details of these patients are presented. Correctly, they indicate that hypoglycemia in children is generally transient and usually responds to relatively simple dietary and pharmacologic measures. Persistent severe hypoglycemia is not common, but presents a dramatic and potentially lethal threat to children with this syndrome. Most centers with an interest in metabolic diseases of infants and children continue to report an alarmingly high percentage of treatment failures and long-term neurologic sequelae. Management of hypoglycemia in the first two weeks of life is directed towards the maintenance of normal serum glucose levels. Hypoglycemia that is persistent but mild and easily controlled may be seen in a variety of metabolic and endocrine disorders such as hypothyroidism and hypopituitarism. When hypoglycemia is severe and persistent beyond the first two weeks of life, an inborn error of metabolism or hyperinsulinism is usually the cause.[1] An inborn error of metabolism is unlikely in the absence of hepatomegaly and can usually be excluded if the serum pH, lactic acid and ammonia levels are within normal limits and the urine is negative for ketones, amino acids and reducing substances.[2] It should be emphasized that in children, and particularly in neonates, with hyperinsulinism the serum insulin levels are rarely very high. If the serum insulin level is 5 $\mu$U per ml or more during hypoglycemia, the diagnosis of hyperinsulinemia should be strongly considered. Hyperinsulinism, which is the most common cause of persistent neonatal hypoglycemia,[2] is diagnosed if an inappropriately high insulin level is found during a period of hypoglycemia. A thorough evaluation frequently produces confusing and equivocal data and unfortunately results in a protracted period of nonoperative management.[3,4] An insulin to glucose ratio greater than 1:2—obtained by placing the insulin value expressed in microunits per milliliter of serum over the glucose level in milligrams per deciliters—during a period of hypoglycemia is a most valuable laboratory discriminant when deciding whether surgical intervention is warranted.[5] Although most investigators have concluded that early surgical intervention for hyperinsulinism is appropriate, the documentation of this disorder may be exceedingly difficult in some patients.

Hyperinsulinism may result from discrete islet cell adenomas or the diffuse pancreatic lesions of microadenomatosis, islet cell hyperplasia or nesidioblastosis. In nesidioblastosis, islet cells are found within the ductal epithelium and are believed to represent a persistence of fetal histology.[6-9] The unresponsiveness of fetal $\beta$-cells to changes in serum glucose levels in the absence of local secretory regulation found in normal islet cells results in the excess insulin secretion seen in nesidioblastosis.[8-11] Results in these patients support the observation that surgical treatment is more effective for localized disease than for diffuse islet cell abnormalities.[12] Adenomatous disease may only represent another morphologic variation of the single fundamental lesion. Furthermore, there are no clinical or laboratory discriminates of significant accuracy to establish a pathologic diagnosis that might alter either the decision to operate or the limits of resection. Regardless of the pathologic diagnosis, the decision must be to control the glucose level with drug or surgical therapy—in small babies, the sooner the better.

These clinical and pathologic considerations support a unified surgical approach to hyperinsulinism. All children with documented hyperinsulinism are candidates for an immediate operation, regardless of the anticipated islet cell abnormalities. Furthermore, the low mortality and morbidity of an operation justify doing it immediately in hyperinsulinemic patients and also in those patients who are too unstable to withstand a protracted evaluation. The authors indicate that visceral angiography, ultrasonography and computed tomography have not been helpful and should not be routinely applied. I concur.

The frequency with which persistent postoperative hypoglycemia is observed in patients with diffuse pancreatic disease demands that surgical therapy be appropriately extensive at the initial procedure. Total pancreatectomy is rarely indicated and should not be done at the initial procedure. Although the technique of total pancreatectomy for hypoglycemia emphasizes leaving tissue on the duodenum, in patients who require this procedure, permanent exocrine and endocrine insufficiencies will usually develop.[12]

The recommendation that the first surgical procedure should consist of a 90% pancreatectomy, consisting of removing all of the pancreas distal to the right side of the superior mesenteric artery, the uncinate process and most of the pancreatic head and

leaving approximately a third of the pancreatic head attached to the duodenum, is attracting more proponents.[2,4,13]

If in the early postoperative period hypoglycemia continues, the patient should be returned to the operating room for a total pancreatectomy without duodenectomy.[4,12]

The authors have correctly emphasized the importance of the spleen, and have stated the dictum that it should be preserved when at all possible.[14]

JOHN R. CAMPBELL, MD
*Division of Pediatric Surgery*
*Department of Surgery*
*Oregon Health Sciences University*
*School of Medicine*
*Portland*

#### REFERENCES

1. Thomas CG Jr, Underwood LE, Carney CN, et al: Neonatal and infantile hypoglycemia due to insulin excess: New aspects of diagnosis and surgical management. Ann Surg 1977; 185:505-517

2. Schiller M, Krausz M, Meyer S, et al: Neonatal hyperinsulinism—Surgical and pathologic considerations. J Pediatr Surg 1980; 15:16-20

3. Finegold DN, Stanley CA, Baker L: Glycemic response to glucagon during fasting hypoglycemia: An aid in the diagnosis of hyperinsulinism. J Pediatr 1980; 96:257-259

4. Campbell JR, Rivers SP, Harrison MW, et al: Treatment of hypoglycemia in infants and children—Surgical considerations. Am J Surg 1983; 146:21-28

5. Castro A, Buist NRM: The insulin-glucose ratio in children with islet cell tumors of the pancreas. Clin Biochem 1974; 7:81-87

6. Knight J, Garvin PJ, Davis RK, et al: Nesidioblastosis in children. Arch Surg 1980; 115:880-882

7. Schwartz SS, Rich BH, Lucky AW, et al: Familial nesidioblastosis: Severe neonatal hypoglycemia in two families. J Pediatr 1979; 95:44-53

8. Shermeta DW, Mendelsohn G, Haller JA Jr: Hyperinsulinemic hypoglycemia of the neonate associated with persistent fetal histology and function of the pancreas. Ann Surg 1980; 191:182-186

9. Yakovac WC, Baker L, Hummeler K: Beta cell nesidioblastosis in idiopathic hypoglycemia of infancy. J Pediatr 1971; 79:226-231

10. Hirsch HJ, Loo S, Evans N, et al: Hypoglycemia of infancy and nesidioblastosis. Studies with somatostatin. N Engl J Med 1977; 296:1323-1326

11. Grotting JC, Kassel S, Dehner LP: Nesidioblastosis and congenital neuroblastoma: A histologic and immunocytochemical study of a new complex neurocristopathy. Arch Pathol Lab Med 1979; 103:642-646

12. Harken AH, Filler RM, Avruskin TW, et al: The role of 'total' pancreatectomy in the treatment of unremitting hypoglycemia of infancy. J Pediatr Surg 1971; 6:284-289

13. Moazam F, Rodgers BM, Talbert JL, et al: Near-total pancreatectomy in persistent infantile hypoglycemia. Arch Surg 1982; 117:1151-1154

14. Eraklis AJ, Filler RM: Splenectomy in childhood: A review of 1,413 cases. J Pediatr Surg 1972; 7:382-388

## Primary Care—Does It Have a Future?

PRIMARY CARE is very much in the limelight these days. It is actively espoused by the family practice movement, and general internal medicine, pediatrics and obstetrics/gynecology are placing increasing emphasis on what is now being called primary care. The federal government has begun to shift some of its emphasis and support from training specialists and subspecialists to training for primary care. Primary care is seen as the entry point where a patient has first contact with the health care system and from whence he or she is referred to whatever specialists or subspecialists may be needed. It is also viewed as a place where ongoing care is easily coordinated and continuity of care can be achieved. Moreover, it is not lost on the payors for care that a primary care physician is in a strong position to decide upon the kind and amount of care that is given, and therefore what it will cost. Thus there is a growing effort to place a primary care physician in the position of "gatekeeper" with an incentive and responsibility to consider costs when deciding what should be done for a patient.

One might at first think that primary care and primary care physicians are something new, but they are not. Primary care has been there all the time and physicians have rendered it to their patients. But for many years the focus in medical education and medical practice has been on the training of specialists and subspecialists, and medical practice became, almost de facto, divided into specialties and subspecialties. Patients, physicians and patient care all tended to become compartmentalized. But in recent years there have been countervailing forces. Perhaps most important is a growing student interest in the broader and more human aspects of patient care that began more than a decade ago. Then there was coming to be a surfeit, if not a glut, of physicians with far too many specialists, and a perception that there were far too few generalists or primary care physicians. Too many patients were shopping around for their own specialists; many were seeing several specialists at once and, for better or worse, in effect prescribing their own treatment. Another important countervailing force has been the modern development of primary care and the role of the primary care physician. This has been notably assisted by a government that has been reducing its support of specialty and subspecialty training while increasing its support for the training of health professionals for primary care.

Besides being the entry point, and now being looked upon by some as the gatekeeper for patient care, the primary care movement has shown a special interest, not only in the more common ailments to which the flesh is heir, but also in the effect of illness upon a patient and the family, the effect of illness upon the interaction of a patient with his or her environment and the role of the family and others in helping to overcome the illness and its effects. Again this is not new, but the emphasis on it has been much greater than has been the case in the training and practice of many specialists and subspecialists. But is this enough, or is there more that primary care could be interested in? Is it enough to assure that primary care does indeed have a future as a discipline in medical education and patient care?

One senses that a genuine discipline is needed. But what might it be? Most of the science and technology in patient care is subsumed under one or another of the specialties or subspecialties. Research into health care delivery is being explored in terms of primary care, but somehow seems to miss the main focus of interest. Yet research, and good research, is needed to support an academic discipline and to secure it a respected position among scientific and technologic specialty peers in patient care. This will be essential if primary care, as it is coming to be known, is to have the future it could have, and probably deserves.

Primary care is above all an interaction between a doctor and a patient, and continuing care has to be a continuation of this interaction. To be sure, this interaction occurs between doctor and patient in all specialties, but too often in these specialties it may have second place to technological interventions. In primary care, however, the opposite may more likely be the case, and the human interaction may play the more important role with the technological interventions more subservient. There has been little scientific or quantitative study of this all-important topic. There is need objectively to address the phenomenon of the doctor-patient relationship, the skills that can be developed and used within it, the components of what has been called the art of medicine, and the need to relate these to patient and physician satisfaction, and to health care outcomes, particularly in primary care, where so much of the emphasis is on human interaction.

The pendulum seems to be swinging. There is a growing sense that modern medical science and its technology are not everything in patient care. While primary care is nothing new, a renewed emphasis on it, and what it is trying to do, could be the beginning of a new understanding of the phenomena involved in that very special interaction between doctor and patient that is, after all, the most essential ingredient in patient care.

MSMW

# Case Reports

## The Corticotropin-Releasing Factor Test in the Diagnosis of Ectopic ACTH Secretion

ENRICO CAGLIERO, MD
MARA LORENZI, MD
*San Diego*

THE DIFFERENTIAL DIAGNOSIS between pituitary Cushing's syndrome (Cushing's disease) and ectopic adrenocorticotropic hormone (ACTH) secretion can be deceptive because the sensitivity and specificity of the traditional pharmacologic tests are not optimal. Recently the corticotropin-releasing factor (CRF) stimulation test has been proposed as a helpful tool in the differential diagnosis of Cushing's syndrome. We report a case that underlines the usefulness of this new test.

### Report of a Case

A 73-year-old woman was admitted to a local hospital in September 1984 with weakness, central obesity, type II diabetes mellitus of new onset, increase in facial hair and easy bruising. Her history was remarkable for resection of a Dukes' B2 adenocarcinoma of the colon in September 1980, new-onset sixth cranial nerve palsy in October 1983 and abnormal liver function since February 1984. She had been taking chlorpropamide, furosemide and potassium chloride. On physical examination she showed occasional disorientation, multiple ecchymoses, hirsutism and central obesity. The liver was enlarged but nontender; there was left sixth cranial nerve palsy and severe bilateral proximal lower extremity weakness. Laboratory values included normal electrolytes; aspartate aminotransferase (formerly SGOT) 66, alanine aminotransferase (formerly SGPT) 72, lactic dehydrogenase 736 and alkaline phosphatase 332 IU per liter; total bilirubin 1.5 mg per dl. Plasma cortisol levels were elevated (28 and 30 μg per dl in the afternoon), as were the plasma ACTH levels (118 and 139 pg per ml), and the urinary 17-hydroxycorticoids failed to suppress with the administration of both 2 mg of dexamethasone (from a base line of 12.0 to 13.2 mg per 24 hours) and 8 mg of dexamethasone (12.9 mg per 24 hours). These data were interpreted as suggestive of ectopic ACTH secretion. Further studies included chest and abdominal computed tomographic (CT) scans that showed bilateral adrenal enlargement, two lucencies in the liver (unchanged since 1981) and a questionable thickness in the tail of the pancreas. CT-scan-guided pancreatic biopsy yielded only a few normal pancreatic cells.

At this juncture the possibility of a pituitary source of ACTH was reconsidered. A "very high" dexamethasone test (32 mg) showed suppression of the 17-hydroxycorticoids (from a base line of 12.0 to 5.8 mg per 24 hours), and a metyrapone test showed appropriate increase of plasma 11-deoxycortisol to 24 μg per ml. These results were interpreted as being consistent with pituitary Cushing's syndrome, and the patient was transferred to the University of California, San Diego, Medical Center on October 28, 1984. A CRF stimulation test (1 μg per kg body weight) showed no increase in plasma cortisol levels (35 μg per dl at base line and 32 to 36 μg per dl up to 120 minutes after CRF was given) and bilateral inferior petrosal sinus catheterization showed no gradient in ACTH levels (106 pg per ml in the right sinus, 150 pg per ml in the left sinus and 133 pg per ml in the inferior vena cava). A liver biopsy yielded malignant cells, and a regimen of aminoglutethimide and hydrocortisone was started. Her condition rapidly worsened and she died on November 15, 1984. An autopsy showed a metastatic poorly differentiated adenocarcinoma originating from the tail of the pancreas and there was no evidence of pituitary adenoma.

ABBREVIATIONS USED IN TEXT
ACTH = adrenocorticotropic hormone
CRF = corticotropin-releasing factor
CT = computed tomography

### Discussion

The pharmacologic studies used for the differential diagnosis between Cushing's disease and ectopic ACTH secretion are based on the fact that pituitary tumor cells are under a certain degree of control from the hypothalamic-pituitary-adrenal axis while ectopic ACTH-producing cells lack such control. Thus, while patients with Cushing's disease tend to have suppressibility of ACTH secretion by high doses of dexamethasone and responsiveness to inhibition of 11-hydroxylase by metyrapone, in patients with ectopic ACTH secretion,

TABLE 1.—*Sensitivity and Specificity of Pharmacologic Tests Used in the Differential Diagnosis of Cushing's Disease Versus Ectopic ACTH Syndrome*

| Pharmacologic Tests | Response | Patients, Percent | Patients, Number | 95% Confidence Limits, Percent |
|---|---|---|---|---|
| *High-Dose Dexamethasone** | | | | |
| Cushing's disease | Suppression | 90 | ... | ... |
| | No suppression | 10 | ... | ... |
| Ectopic ACTH syndrome | Suppression | 20 | 12 | 10-30 |
| | No suppression | 80 | 48 | 70-90 |
| *Metyrapone Test** | | | | |
| Cushing's disease | Response | 87 | 150 | 82-92 |
| | No response | 13 | 23 | 8-18 |
| Ectopic ACTH syndrome | Response | 48 | 16 | 31-65 |
| | No response | 52 | 17 | 34-68 |
| *CRF Test†* | | | | |
| Cushing's disease | Response | 94 | 46 | 68-100 |
| | No response | 6 | 3 | 0-32 |
| Ectopic ACTH syndrome | Response | 7 | 1 | 0-20 |
| | No response | 93 | 13 | 80-100 |

ACTH=adrenocorticotropic hormone, CRF=corticotropin-releasing factor

*From Findling et al,[6] Sindler et al,[7] Imura et al,[8] Crapo[9] and Howlett et al.[10]
†From Chrousos et at,[11,12] Rohrmoser et al,[13] Orth et al, [14] Müller et al,[15] Nakahara et al,[16] Pieters et al[17] and Lytras et al.[18]

(Cagliero E, Lorenzi M: The corticotropin-releasing factor test in the diagnosis of ectopic ACTH secretion. West J Med 1987 May; 146:614-615)

From the Department of Medicine, Division of Endocrinology and Metabolism, University of California, San Diego, Medical Center, San Diego.

Reprint requests to Enrico Cagliero, MD, UCSD Medical Center H-811-C, 225 Dickinson St, San Diego, CA 92103.

no suppressibility with dexamethasone and no response to metyrapone are expected. The interpretation of such tests should, however, take into account—in addition to the intra-assay and interassay coefficient of variation for the analytical determinations—that the sensitivity and specificity for Cushing's disease of both these tests are less than 100%. As shown in Table 1, among patients with the ectopic ACTH syndrome, 48% show an apparent response to metyrapone and 20% to dexamethasone.

To achieve a better separation of pituitary versus ectopic sources of ACTH, some authors advocate the use of higher doses of dexamethasone (32 mg) in patients who fail to respond to the standard 8-mg test.[1-3] We warn about using such a maneuver, which is based on a single case report,[4] has not been systematically evaluated and may, as in the case of our patient, lead to an erroneous diagnosis. The availability of CRF, the hypothalamic polypeptide that modulates pituitary ACTH secretion, provides a novel tool for the differential diagnosis of Cushing's syndrome.[5] Review (Table 1) of the 49 published cases of Cushing's disease tested with CRF shows that 46 (94%) patients showed a response while only 3 (6%) patients showed no response and, of the 14 patients with ectopic ACTH secretion, 13 showed no response to CRF and 1 patient showed some responsiveness that was, however, not reproducible. If further data confirm this trend, the CRF test could become very useful in the etiologic diagnosis of Cushing's syndrome and would have a greater sensitivity and specificity than the standard 8-mg dexamethasone test. The addition of this simple test to the diagnostic evaluation could in some patients reduce the need for more invasive and expensive diagnostic procedures such as inferior petrosal sinus catheterization.

#### REFERENCES


1. West CD, Meikle AW: Laboratory tests for the diagnosis of Cushing's syndrome and adrenal insufficiency and factors affecting those tests, chap 94, *In* De Groot LJ, Cahill GF, Odell WD, et al (Eds): Endocrinology, Vol 2. New York, Grune & Stratton, 1979, pp 1171-1172

2. Tyrrell JB, Forsham PH: Glucocorticoids and adrenal androgens, chap 9, *In* Greenspan FS, Forsham PH (Eds): Basic & Clinical Endocrinology, 4th Ed. Los Altos, Lange Medical Publications, 1983, pp 258-294

3. Wand GS, Ney RL: Disorders of the hypothalamic-pituitary-adrenal axis. J Clin Endocrinol Metab 1985; 14:33-53

4. Linn JE, Bowdoin B, Farmer A, et al: Observations and comments on failure of dexamethasone suppression. N Engl J Med 1967; 277:403-405

5. Chrousos GP, Schuermeyer TH, Doppman J, et al: Clinical applications of corticotropin-releasing factor. Ann Intern Med 1985; 102:344-358

6. Findling JW, Aron DC, Tyrrell JB, et al: Selective venous sampling for ACTH in Cushing's syndrome: Differentiation between Cushing disease and the ectopic ACTH syndrome. Ann Intern Med 1981; 94:647-652

7. Sindler BH, Griffing GT, Melby JC: The superiority of the metyrapone test versus the high-dose dexamethasone test in the differential diagnosis of Cushing's syndrome. Am J Med 1983; 74:657-662

8. Imura H, Matsukura S, Yamamoto H, et al: Studies on ectopic ACTH-producing tumors. Cancer 1975; 35:1430-1437

9. Crapo L: Cushing's syndrome: A review of diagnostic tests. Metabolism 1979; 28:955-977

10. Howlett TA, Rees LH, Besser GM: Cushing's syndrome. Clin Endocrinol Metab 1985; 14:911-945

11. Chrousos GP, Schulte HM, Oldfield EH, et al: The corticotropin-releasing factor stimulation test. N Engl J Med 1984; 310:622-626

12. Chrousos GP, Nieman L, Nisula B, et al: Corticotropin-releasing factor stimulation test. N Engl J Med 1984; 311:472-473

13. Rohrmoser B, Lüdecke DK, Scriba PC: Inconsistent stimulation of plasma ACTH through corticotropin-releasing factor in a patient with central Cushing's disease due to pituitary adenoma. Klin Wochenschr 1985; 63:475-477

14. Orth DN, DeBold CR, DeCherney GS, et al: Pituitary microadenomas causing Cushing's disease respond to corticotropin-releasing factor. J Clin Endocrinol Metab 1982; 55:1017-1019

15. Müller OA, Stalla GK, von Werder K: Corticotropin releasing factor: A new tool for the differential diagnosis of Cushing's syndrome. J Clin Endocrinol Metab 1983; 57:227-229

16. Nakahara M, Shibasaki T, Shizume K, et al: Corticotropin-releasing factor test in normal subjects and patients with hypothalamic-pituitary-adrenal disorders. J Clin Endocrinol Metab 1983; 57:963-968

17. Pieters GFFM, Hermus ARMM, Smals AGH, et al: Responsiveness of the hypophyseal-adrenocortical axis to corticotropin-releasing factor in pituitary-dependent Cushing's disease. J Clin Endocrinol Metab 1983; 57:513-516

18. Lytras N, Grossman A, Perry L, et al: Corticotropin releasing factor: Responses in normal subjects and patients with disorders of the hypothalamus and pituitary. Clin Endocrinol (Oxf) 1984; 20:71-84


# Acquired Immunodeficiency Syndrome Presenting as Schizophrenia


MICHAEL A. CUMMINGS, MD
KATHRYN L. CUMMINGS, RN
MARK H. RAPAPORT, MD
JOSEPH H. ATKINSON, MD
IGOR GRANT, MD
*San Diego*


SEVERAL INVESTIGATORS have reported affective and psychotic symptoms with the acquired immunodeficiency syndrome (AIDS). Nurnberg and co-workers reported the case of a 28-year-old man with AIDS who presented with command hallucinations, persecutory delusions, anorexia, a 13.6-kg weight loss (30 lb), anhedonia, abulia, middle insomnia, psychomotor retardation and impaired recent memory.[1] Hoffman reviewed two AIDS cases that had in common a psychiatric presentation and diffuse cerebral atrophy indicated by computed tomography.[2] One case was characterized as progressive dementia and the other as transient acute encephalopathy. Kermani and associates identified a triad of mood disturbance, thought disorder with grandiose delusions and severe memory deficits in a series of three patients with AIDS.[3] Subsequently, Kermani and colleagues described the case of an AIDS patient who presented with manic features before development of cognitive and memory impairment,[4] while Thomas and co-workers reported seeing a 22-year-old patient with AIDS who had a paranoid psychosis but normal cognitive and memory functions.[5]

We report a case further illustrating the protean presentation of psychiatric signs and symptoms in AIDS patients and define one pathway—a natural history culminating in dementia. The case is remarkable because of a prolonged course that began with subtle organicity, was punctuated by psychotic decompensation and progressed to profound dementia.

## Report of a Case

The patient, a 32-year-old single, bisexual man, was brought to the psychiatric emergency service by his sister. She stated that for the past nine months he had increasing apathy, social withdrawal to the point of almost total isolation and bizarre behavior such as urinating in public. The initial


(Cummings MA, Cummings KL, Rapaport MH, et al: Acquired immunodeficiency syndrome presenting as schizophrenia. West J Med 1987 May; 146:615-618)



From the Department of Psychiatry, Veterans Administration Medical Center, San Diego, and the Department of Psychiatry, University of California, San Diego, School of Medicine, La Jolla.



This work was supported in part by award SA-325 to Igor Grant, MD, from the Medical Research Service of the Veterans Administration and from the Clinical Research Center (National Institute of Mental Health [NIMH] grant 5 P50 MH-30914-09) and Clinical Research Fellowship Program (NIMH grant MH-18399-01), Department of Psychiatry, University of California, San Diego.



Reprint requests to Igor Grant, MD, Psychiatry Service (116), VA Medical Center, San Diego, CA 92161.

ABBREVIATIONS USED IN TEXT

AIDS = acquired immunodeficiency syndrome
CMV = cytomegalovirus
CNS = central nervous system
HIV = human immunodeficiency virus

interview, using the patient and his sister as informants, revealed that he had a 12-month history of a colitis partially responsive to treatment with sulfasalazine (Azulfidine), which shortly preceded the onset of apparent apathy, withdrawal and unusual behavior. Six months before evaluation he had received a short course of amitriptyline hydrochloride (Elavil) for a depressed mood attributed to pain and diarrhea from colitis and to his dissatisfaction with his work. His mood improved. Three months before evaluation he lost his job as a computer data processor because of emotional lability, decreased concentration and diminished productivity. He returned home to live with his parents, who noted his inattentiveness, peculiar behavior and bizarre grimacing. He became increasingly agitated and confided with his married sister that he feared he was losing his mind. During their parents' vacation, the sister became alarmed by his more apparent agitation and eccentric behavior and brought him to the emergency department for evaluation.

The patient said he had no history of behavioral or psychiatric problems before the onset of the current illness. This was corroborated by family members, as was the negative family history for psychiatric disorder.

On mental state examination he appeared disheveled but well developed and was agitated and distracted. He exhibited bizarre facial grimacing. His rate of speech was normal. His thinking was impoverished, his associations were moderately loosened and he manifested occasional blocking. His affect was guarded and he smiled or laughed frequently, which was incongruous with verbal content. He said he did not have hallucinations, but he appeared to look at and listen to internally generated stimuli. He admitted to receiving special messages from television programs and music and felt that the family television could cause his thoughts to vanish. He also believed that his intestine was an independent organism that crawled from side to side "like a worm." Suicidal and homicidal ideas were absent.

He was alert and oriented to person, place and time and could follow simple commands. His forward-digit memory span was seven, and he was able to recall three/three objects after five minutes. He named past presidents as Reagan, Carter, Kennedy, Nixon and Truman. He made several subtraction errors on serial sevens. Proverbs were bizarrely interpreted. To "a rolling stone gathers no moss," he responded "let's canoe down the river." "Even monkeys fall out of trees" was interpreted as "cats do, too."

On the basis of a history of bizarre behavior and steady deterioration of functioning, plus a mental state showing psychotic features and disturbance in attention attributed to agitation and thought disorder, a clinical diagnosis of schizophrenia was made in the psychiatric emergency clinic and the patient was admitted to the psychiatry service.

On admission to the psychiatry unit, the findings of a physical examination were significant for a temperature of 37.9°C (100.2°F), cervical and inguinal lymphadenopathy, diffuse rales and rhonchi, diffuse abdominal tenderness without rebound and multiple hyperpigmented, arcuate skin lesions over the upper back and arms consistent with Kaposi's sarcoma. These findings led to the presumptive diagnosis of AIDS, and the patient was transferred to the medical service.

Laboratory evaluation showed normocytic anemia, relative leukopenia in a patient with infection (leukocyte count 4,200 to 6,600 per $\mu$l) and a normal differential without a left shift. His serum lactic dehydrogenase level was elevated at 184 to 288 units per liter, and his $\gamma$-glutamyl transferase level was elevated at 75 to 196 IU per liter. Oropharynx cultures were positive for *Candida albicans* and *Candida krusei*, bronchial washings were positive for *Hemophilus influenzae* and fecal cultures were positive for *Cryptospiridium* and *Campylobacter* organisms. Biopsy of skin lesions yielded a diagnosis of Kaposi's sarcoma. A traumatic lumbar puncture showed a total cerebrospinal fluid protein content of 76 mg per dl, glucose 44 mg per dl and 3 lymphocytes per $\mu$l. Cultures of cerebrospinal fluid specimens were negative for bacteria, results of serology were normal, and cultures for cytomegalovirus (CMV) and antibody titers for *Toxoplasma gondii* were negative. Chest x-ray films were normal. Urine toxicologic tests for hallucinogens, psychostimulants, sedative-hypnotics, narcotics, alcohol and salicylates were negative.

To document the psychiatric presentation more reliably, a psychiatrist trained in administering the National Institute of Mental Health Diagnostic Interview Schedule (DIS, Version III-A)[6] interviewed the patient two days after his transfer. Based on the interview and initial presentation, the patient satisfied criteria for schizophrenia according to the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders*, third edition.

By three weeks after admission, a thorough neuroradiologic and neuropsychological examination was completed. In the first week, clinical reassessment showed more apparent cognitive deficits. A computed tomographic scan of the head showed lateral and third ventricular enlargement consistent with early hydrocephalus. Nuclear magnetic resonance imaging of the head was interpreted as normal.

Neuropsychological assessment confirmed cognitive dysfunction. The patient achieved scaled scores of 8 on the Wechsler Adult Intelligence Scale-Revised digit-span and vocabulary subtests; expected scaled scores given the patient's age and education would be 11 or 12 for each subtest.[7] On the subtest Symbol Digit Paired Associate Learning,[8] the patient scored 7 of 28 correct over four trials; testing of control subjects in our laboratory indicates a normal range of 21 to 28 correct items. On Halstead's Category Test the patient made 95 errors per 208 stimuli. The average score for persons of this patient's age and education is 39, and a score above 50 shows definite impairment.[9,10] Wechsler Memory Scale Visual Reproduction Testing showed profound deficits and delay in completing visual motor tasks.[11] The patient was unable to do trail-making tests and Paced Auditory Addition tests. Overall, neuropsychological testing indicated severe deficits in memory, abstracting ability and visual-motor performance.

The patient's psychiatric clinical presentation had evolved from schizophrenia-like symptoms to a more apparent dementia. Over a four-week period, his speech became less productive and more disorganized, his mood changed from silly to sullen with frequent outbursts of hostility. Ideas of reference and delusional material decreased and he later denied having them. On repeat examination he no longer met

criteria for a current diagnosis of schizophrenia and said he did not have the criterion items for a lifetime diagnosis of this disorder. Deficits in memory and orientation persisted. His agitation diminished after treatment with haloperidol (Haldol), 2 to 4 mg given daily by mouth, and the medication was discontinued before discharge without worsening of symptoms. He said he had no interest in his diagnosis or prognosis, and he ceased confiding in his sister. At first, his parents refused his discharge to home and insisted on institutional care. Information about the low infectivity of human immunodeficiency virus (HIV) and an introduction to support services reassured his parents and they accepted his care. His discharge diagnosis was HIV encephalitis.

He was admitted to hospital four times during the remaining six months of his life for both behavioral and physical complications resulting from opportunistic infections. Treatment of intercurrent infections permitted the patient to return to his parents' care at home. The major problems in management at home were the patient's daytime and nocturnal wanderings away from the house, inattention to personal hygiene and irregular patterns of eating, sleeping and activity. Haloperidol therapy, 2 to 4 mg given daily, helped reduce overactivity and promote regular sleep. His deteriorated judgment (smoking in bed and carelessness with home appliances and automobiles) made supervision necessary. The hospital provided a visiting nurse, and local AIDS Project volunteers supplied supervision at home on weekdays. The family reported that the information and support from the AIDS Project were invaluable, but the patient's severe amnestic state limited his ability to use the counseling services offered. Because of wasting and recurrent infections, he required hospital care during the final two months of life. The encephalitis and his central nervous system (CNS) symptoms were actively evaluated without detection of a treatable causative agent. Cerebral ventricular shunting was felt to be contraindicated because of widespread opportunistic infection. The patient ultimately died of pulmonary complications of AIDS.

An autopsy showed meningoencephalitis with severe ependymitis, ependymal necrosis and subependymal gliosis. Individual astrocytes contained both intranuclear and intracytoplasmic inclusions consistent with cytomegalovirus. The neuropathologic diagnosis was meningoencephalitis, ventriculitis and cytomegalovirus encephalitis.

## Comment

Recent studies show both direct and indirect mechanisms by which AIDS can affect the central nervous system, giving rise to neuropsychiatric signs and symptoms. Indirect mechanisms thus far described include opportunistic infections (such as CMV and toxoplasmosis), primary cerebral lymphoma, secondary cerebral lymphoma, cerebral thromboembolic damage and cerebral hemorrhage.[12-14] With regard to the patient presented here, neither the cause nor the pathogenesis of the subacute encephalitis of AIDS has yet been established. CMV is a leading candidate,[12] and up to a quarter of patients dying with AIDS dementia show neuropathologic evidence of CMV infection. At the same time, neither a subcortical neuropathologic disorder nor clinical dementia correlate very well with evidence of CMV infection, indicating that this herpes virus infection may represent a secondary, superimposed process.[15] For this reason, HIV has become a prime suspect as the etiologic factor in AIDS dementia. Moreover, Ho and associates found direct HIV infection of neural and cerebrospinal fluid in 45 neuropsychiatrically affected AIDS patients.[16] In an immunologic study of serum and cerebrospinal fluid antibodies to HIV in 23 patients suffering AIDS or AIDS-related complex, cerebrospinal fluid antibodies were present in 22 of 23 cases. Of the 23 cases examined, 21 had neuropsychiatric signs and symptoms, suggesting that direct HIV infection of the central nervous system occurs in most neuropsychiatrically affected AIDS patients.[17]

Infection with HIV can lead to several medical outcomes including the development of immunity, asymptomatic immunodeficiency, autoimmune thrombocytopenia, AIDS-related complex, a wasting syndrome and AIDS.[18] Our case and those reviewed above suggest that HIV infection can also present in a psychiatrically protean fashion. Our own case showed a schizophrenia-like presentation, but affective and other behavioral disorders have also been reported. Indeed, our patient's early depressive symptoms may have represented a response to subtle cognitive impairment as well as to the burden of colitis. Although AIDS-related brain disease often appears to be the cause of such psychopathologic features, it is also recognized that AIDS may give rise to psychiatric illness as a consequence of the psychosocial stress induced by this devastating lethal illness.[19-21] While this patient showed a virulent and progressively deteriorating course, it should not be assumed that all patients with direct or indirect CNS effects of AIDS irrevocably decline. Aggressive diagnosis and treatment of CNS disease, such as toxoplasmosis or cryptococcosis, are effective, and, indeed, supportive care helped our patient to function at home until his final admission to hospital.

The ability of AIDS to mimic diverse psychiatric syndromes will require vigilance by psychiatrists and other physicians as the AIDS epidemic continues. Those persons presenting with psychiatric signs and symptoms who are identified as belonging to a high-risk group should undergo careful neurologic, neuropsychological, physical and laboratory evaluation as part of the initial and follow-up psychiatric assessments. The differential diagnosis of major psychiatric findings (psychosis, major depression) should include organic brain dysfunction as well as functional psychiatric illness. Abnormalities in neuropsychological or neuroradiologic tests may confirm the diagnosis, but an absence of positive findings should not exclude it: abnormalities on electroencephalogram, computed tomographic scan and magnetic resonance imaging are not universal, and formal neuropsychological batteries can yield equivocal results. Serial examinations may be necessary to detect underlying morphologic and cognitive disturbances responsible for the psychiatric symptoms in individual cases. The advent of promising new treatments for AIDS makes such careful assessment essential. In the future, longitudinal study of HIV-infected patients will be necessary to clarify the incidence, prevalence and natural history of psychiatric signs and symptoms in patients with AIDS.

### REFERENCES

1. Nurnberg HG, Prudic J, Fiori M, et al: Psychopathology complicating acquired immune deficiency syndrome (AIDS). Am J Psychiatry 1985; 141:95-96

2. Hoffman RS: Neuropsychiatric complications of AIDS. Psychosomatics 1984; 25:393-395, 399-400

3. Kermani E, Drob S, Alpert M: Organic brain syndrome in three cases of acquired immune deficiency syndrome. Compr Psychiatry 1984; 25:294-297

4. Kermani EJ, Borod JC, Brown P, et al: New psychopathologic findings in AIDS: Case report. J Clin Psychiatry 1985; 46:240-241

5. Thomas CS, Toone BK, El Komy A, et al: HTLV III and psychiatric disturbance (Letter). Lancet 1985; 1:395-396

6. Robins LN, Helzer JE, Croughan J, et al: National Institute of Mental Health

Diagnostic Interview Schedule—Its history, characteristics, and validity. Arch Gen Psychiatry 1981; 33:381-389

7. Wechsler D: The Measurement and Appraisal of Adult Intelligence. Baltimore, Williams & Wilkins, 1958

8. Brandt J, Butters N, Ryan C, et al: Cognitive loss and recovery in long-term alcohol abusers. Arch Gen Psychiatry 1983; 40:435-442

9. Heaton RK, Grant I, Matthews CG: Differences in neuropsychological test performance associated with age, education, and sex, *In* Grant I, Adams KM (Eds): Neuropsychological Assessment of Neuropsychiatric Disorders. New York, Oxford University Press, 1986, pp 100-120

10. Reitan RM, Davison L: Clinical Neuropsychology: Current Status and Applications. New York, VH Winston & Sons, 1974

11. Wechsler D: A standardized memory scale for clinical use. J Psychol 1945; 19:87-95

12. Snider WD, Simpson DM, Nielsen J, et al: Neurological complications of acquired immune deficiency syndrome: Analysis of 50 patients. Ann Neurol 1983; 14:403-418

13. Lowenstein RJ, Sharfstein SS: Neuropsychiatric aspects of acquired immune deficiency syndrome. Int J Psychiatry 1983-1984; 13:255-260

14. Wetli CV, Weiss SD, Cleary TJ, et al: Fungal cerebritis from intravenous drug abuse. J Forensic Sci 1984; 29:260-268

15. Navia BA, Eun-Sook C, Petito CK, et al: The AIDS dementia complex: II. Neuropathology. Ann Neurol 1986; 19:525-535

16. Ho DD, Rota TR, Schooley RT, et al: Isolation of HTLV-III from cerebrospinal fluid and neural tissues of patients with neurologic syndromes related to the acquired immunodeficiency syndrome. N Engl J Med 1985; 313:1493-1497

17. Resnick L, di Marzo-Veronese F, Schupbach J, et al: Intra-blood-brain-barrier synthesis of HTLV-III-specific IgG in patients with neurologic symptoms associated with AIDS or AIDS-related complex. N Engl J Med 1985; 313:1498-1504

18. Mathur-Wagh U, Mildvan DP: Prodromal syndromes in AIDS. Ann NY Acad Sci 1984; 437:184-191

19. Perry SW, Tross S: Psychiatric problems of AIDS inpatients at the New York Hospital: Preliminary report. Public Health Rep 1984; 99:200-205

20. Forstein M: The psychosocial impact of the acquired immunodeficiency syndrome. Semin Oncol 1984; 11:77-82

21. Holland JC, Tross S: The psychosocial and neuropsychiatric sequelae of the acquired immunodeficiency syndrome and related disorders. Ann Intern Med 1985; 103:760-764

# A 32-Year-Old Man With the Acquired Immunodeficiency Syndrome and Pneumococcal Meningitis

DIANE V. HAVLIR, MD
MALLORY D. WITT, MD
MERLE SANDE, MD
*San Francisco*

THE ACQUIRED immunodeficiency syndrome (AIDS) is characterized by unusual microbiologic and neoplastic disease in patients infected with the human immunodeficiency virus (HIV).[1] Not unexpectedly, infections with these unusual microbiologic organisms may present atypically in an AIDS patient, an immunologically impaired host. In this report, a case of pneumococcal meningitis in a patient with AIDS is reported to emphasize that a common community organism, *Streptococcus pneumoniae*, may also have an atypical presentation in patients with AIDS. Prompt evaluation—but not empiric therapy—for bacterial meningitis in an AIDS patient is recommended.

(Havlir DV, Witt MD, Sande M: A 32-year-old man with the acquired immunodeficiency syndrome and pneumococcal meningitis. West J Med 1987 May; 146:618-619)

From the Department of Medicine, Moffitt Hospital, University of California, San Francisco (Drs Havlir and Witt), School of Medicine, and San Francisco General Hospital Medical Center (Drs Sande and Havlir).

Reprint requests to Diane V. Havlir, MD, Department of Internal Medicine, San Francisco General Hospital, 1001 Potrero Ave, San Francisco, CA 94107.

ABBREVIATIONS USED IN TEXT

AIDS = acquired immunodeficiency syndrome
CNS = central nervous system
CSF = cerebrospinal fluid
HIV = human immunodeficiency virus
UCSF = University of California, San Francisco

## Report of a Case

The patient, a 32-year-old homosexual man with AIDS, was seen because of fever and an altered mental state. Kaposi's sarcoma was diagnosed eight months before admission. Three months before admission, the patient presented with an altered mental state and was found to have cryptococcal meningitis with positive cerebrospinal fluid (CSF) cultures and a cryptococcal antigen titer of 1:512. He was treated with amphotericin B and flucytosine with improvement of his mental state and clearing of CSF cultures.

The patient lived alone and friends reported that his mental state declined during the week before admission. The patient said he did not have headaches, a stiff neck or photophobia. He reported having diarrhea for three days, with 20 bowel movements per day.

The patient had a history of syphilis, gonorrhea, *Clostridium difficile* colitis, thrush and shigellosis. His medications included ketoconazole, acetaminophen with codeine and Lomotil.* He did not smoke or drink alcohol, but he had been reported to abuse narcotics parenterally.

On physical examination he was lethargic and cachectic. His blood pressure was 98/50 mm of mercury and the pulse rate was 100 beats per minute with no orthostatic changes. His temperature was 40°C (104°F). Multiple violaceous lesions consistent with Kaposi's sarcoma were present on the skin of the face and extremities. His head showed no evidence of trauma, and his tympanic membranes were clear. He had a coated white tongue. His fundi were normal, and his neck was supple. There was no Kernig's or Brudzinski's sign. Results of respiratory tract, cardiovascular and abdominal examinations were within normal limits. The patient was oriented to name and place but not to month or year. He followed commands slowly but appropriately. The findings of the rest of the neurologic examination were nonfocal.

Laboratory values included a leukocyte count of 4,600 per $\mu$l, with a differential of 60% segmented forms, 30% band forms, 4% lymphocytes and 5% monocytes. The hematocrit was 30% (SI unit [Système International d'Unités] 0.30), serum sodium concentration was 135 mEq per liter (or mmol per liter) and potassium concentration was 2.2 mEq per liter (or mmol per liter). The value of blood urea nitrogen was 43 mg per dl (15.4 mmol per liter), serum creatinine was 2.2 mg per dl (195 $\mu$mol per liter) and glucose was 95 mg per dl (5.2 mmol per liter). The chest radiograph, electrocardiogram and urinalysis results were normal.

The patient received vigorous fluid and electrolyte replacement. He had no improvement of his mental state when given 1.6 mg of naloxone hydrochloride intravenously. A lumbar puncture was done and showed an opening pressure of 510 mm of water, with 410,000 erythrocytes and 1,400 leukocytes per $\mu$l, with 83% segmented forms, 10% lymphocytes and 7% monocytes. The CSF glucose concentration was 28 mg per dl and the protein was 1,500 mg per dl. A Gram's

*A combination product containing diphenoxylate hydrochloride and atropine sulfate.

stain of the CSF showed many polymorphonuclear leukocytes and many Gram-positive diplococci in pairs.

The patient was treated with a regimen of penicillin, 4 million units given intravenously every four hours. Blood and CSF cultures grew *S pneumoniae* in less than 24 hours. Cerebrospinal fluid fungal culture showed no growth. Within six hours of admission, the patient became obtunded. On the third hospital day he had generalized seizures that responded to the administration of phenytoin (Dilantin) and phenobarbital. On the eighth hospital day he began to respond to commands, and his base-line mental state gradually returned by the tenth hospital day. He received a total of two weeks of intravenous penicillin G therapy.

## Discussion

Central nervous system (CNS) infections in patients with AIDS are common. In a recent review of 352 AIDS patients at the University of California, San Francisco (UCSF), 105 infections of the CNS were reported.[2] The most common infections seen were viral-like syndromes, predominantly manifested as a subacute encephalitis and atypical meningitis. The recent identification of HIV in the CNS in cases of neurologic disease suggests that the HIV virus may cause the AIDS-related meningitis and encephalitis.[3]

*Cryptococcus neoformans* was the most common etiologic agent identified in nonviral meningitis in the UCSF series, being reported in 16 of 128 cases. In patients with AIDS, cryptococcal meningitis may not present with the classic syndrome of fever, headache, stiff neck and photophobia. In addition, cerebrospinal fluid may not show the expected changes in cell counts and chemistries.[4] Therefore, a high index of suspicion for cryptococcal disease in an AIDS patient must be present, even in the absence of the expected clinical findings.

No cases of bacterial meningitis were reported in the UCSF series. Recent reports, however, highlight the importance of bacterial infections in the AIDS population as a cause of bacteremia and pulmonary disease.[5-8] The predisposition to infection with encapsulated organisms such as *S pneumoniae* and *Hemophilus influenzae* is thought to result from impaired B-cell immunity.[9,10]

The patient presented here did not show classic signs of meningitis, yet his spinal fluid was grossly infected with *S pneumoniae*. This case shows that this encapsulated organism may cause meningitis in an AIDS patient, and that its presentation, like that seen in cryptococcal disease, may be atypical.

This case raises the question of whether to initiate antibiotic treatment in a patient known to have AIDS who presents with an altered mental state. Polsky and co-workers conclude that *S pneumoniae* and *H influenzae* are significant enough pathogens to warrant empiric antibiotic coverage for pulmonary infiltrates until a definite organism can be identified.[7] At present, based on the epidemiology of CNS infections in AIDS patients, we do not feel empiric coverage for bacterial CNS infections is warranted. As this case shows, however, an altered mental state should be rapidly evaluated and a CSF specimen promptly examined for common and opportunistic pathogens because bacterial meningitis is a treatable cause of an altered mental state in a patient with AIDS.

### REFERENCES

1. CDC. Classification system for human T-lymphotrophic virus type III/lymphadenopathy-associated virus infections. MMWR 1986; 35:334-339

2. Levy R, Bredesen DE, Rosenblum ML: Neurologic manifestations of the acquired immunodeficiency syndrome (AIDS): Experience at UCSF and review of the literature. J Neurosurg 1985; 62:473-479

3. Ho DD, Rota RR, Schooley RT, et al: Isolation of HTLV-III from cerebrospinal fluid and neural tissues of patients with neurologic syndrome related to the acquired immunodeficiency syndrome. N Engl J Med 1985; 313:1493-1504

4. Zuger A, Louie E, Holzman RS, et al: Cryptococcal disease in patients with the acquired immunodeficiency syndrome. Ann Intern Med 1986; 104:234-240

5. Simberkoff MS, El Sadr W, Schiffman G, et al: *Streptococcus pneumoniae* infections and bacteremia in patients with acquired immunodeficiency syndrome, with report of a pneumococcal vaccine failure. Am Rev Respir Dis 1984; 130:1174-1176

6. White S, Tsua E, Waldhorn RE, et al: Life-threatening bacterial pneumonia in male homosexuals with laboratory features of the acquired immunodeficiency syndrome. Chest 1985; 87:486-488

7. Polsky B, Gold J, Whimberg E, et al: Bacterial pneumonia in patients with the acquired immunodeficiency syndrome. Ann Intern Med 1986; 104:38-41

8. Whimberg E, Gold JW, Polsky B, et al: Bacteremia and fungemia in patients with the acquired immunodeficiency syndrome. Ann Intern Med 1986; 104:511-514

9. Lane HC, Masur H, Edgar LC, et al: Abnormalities of B-cell activation and immunoregulation in patients with the acquired immunodeficiency syndrome. N Engl J Med 1983; 309:453-458

10. Ammann AJ, Schiffman G, Abrams D, et al: B-cell immunodeficiency in acquired immune deficiency syndrome. JAMA 1984; 251:1447-1449

# Correspondence

## Alcohol and Other Drug Dependence Among Latinos

To the Editor: I was extremely concerned regarding the Medical Staff Conference "Issues in Latino Health Care" in the February issue.[1] It completely ignored the role of alcohol and other drug dependence as significant problems for the Latino ethnic group. I will cite three references that thoroughly review the subject:

1. Gilbert M, Cervantes R: Patterns and practices of alcohol use among Mexican-Americans: A comprehensive review. Hispanic Journal of Behavioral Sciences 1986; Vol 8:1-60

2. Caetano R: Drinking patterns and alcohol problems among Hispanics in the U.S.: A review. Drug Alcohol Depend 1983; 12:37-59

3. Arredondo R, Weddige RL, Justice CL, et al: Alcoholism in Mexican-Americans: Intervention and treatment. Hosp Community Psychiatry 1987; 38:180-183

Alcohol and drug dependence continues to be a serious problem for the Hispanic ethnic group.

P. JOSEPH FRAWLEY, MD.
*Chief of Staff*
*Schick Shadel Hospital*
*45 E Alamar St*
*Santa Barbara, CA 93105*

### REFERENCE

1. Pérez-Stable EJ: Issues in Latino health care—Medical Staff Conference, University of California, San Francisco. West J Med 1987 Feb; 146:213-218

## Donor Notification for Positive Non-A, Non-B Hepatitis Surrogate Testing

To the Editor: Antibody to hepatitis B core antigen (anti-HBc) is present in the serum of people who have acute or chronic hepatitis B virus infection. It is frequently detectable in people who have recovered from hepatitis B. Recent reports[1,2] suggested a correlation between the presence of anti-HBc in donated blood and the incidence of transfusion-associated non-A, non-B hepatitis (NANBH). These reports prompted the American Association of Blood Banks (AABB) in November 1986 to recommend routine alanine aminotransferase and anti-HBc as surrogate screening tests for all donors to reduce the risk of NANBH transmission through transfusions (E. M. Berkman, MD, letter to American Association of Blood Bank membership, August 15, 1986). On January 20 and 21, 1987, the Food and Drug Administration (FDA) sponsored a workshop concerning the problems of surrogate testing for preventing posttransfusion NANBH. A problem concerns informing the donor as an obligation of the collection center. Confusing the donor with information describing surrogate tests as "not good, but the best tests we have" has led many donor centers to further test donors with a profile of hepatitis B tests.[3] Since physicians to whom the donor might be referred may be uncertain of the donor testing results, it was urged at the FDA workshop that the donor and physician should be provided with advisory literature. Unfortunately there is no current uniformity in retesting the donor, nor advisory information. To understand how to inform the donor, we included the following tests with our polyvalent anti-HBc testing: IgM anti-HBc, anti-hepatitis B surface antigen (anti-HBs) and alanine aminotransferase (ALT).

Our data from the first 100 anti-HBc donors showed one donor who also had IgM anti-HBc. This same donor was hepatitis B surface antigen negative, anti-HBs negative and ALT negative, indicating by the IgM anti-HBc that this donor was possibly infectious for hepatitis B. Two thirds of these donors were positive for anti-HBs and only two had elevated ALT levels that were 2.25 standard deviations above the log mean. The IgM anti-HBc donor notification was to prevent further spread of hepatitis B; however, we do not recommend the use of this test routinely since the yield is less than 1% of anti-HBc positive donors or less than 3 per 10,000 donors. The cost of this test outweighs the benefits of informing an occasional donor.

We are currently deferring all donors who are confirmed true positive anti-HBc since this indicates past or chronic hepatitis B infection, a reason for permanent deferral. We will continue testing for anti-HBs. Those who are anti-HBc and anti-HBs positive are informed by letter, told they have been exposed to hepatitis but are immune (protected) and not to be alarmed. Those who are only anti-HBc positive are told to see a physician for further evaluation. Those who are ALT positive are not permanently deferred but, because it will be an FDA regulation, the units are discarded. We will not permanently defer these donors until we know the sensitivity, specificity and meaning of ALT testing. We feel donor notification for elevated ALT levels could lead to confusion and alarm. It could perhaps provoke enough confusion and anger in the donor for a medical malpractice suit.

DANIEL B. BRUBAKER, DO
*Head of Blood Bank*
SUSIE UKKESTAD, MSMT
*Supervisor, Diagnostic Immunology*
BYRON A. MYHRE, MD, PhD
*Director of Clinical Laboratories*
*Department of Pathology*
*Harbor-UCLA Medical Center*
*1000 West Carson St*
*Torrance, CA 90509*

### REFERENCES

1. Koziol DE, Holland PV, Alling DW, et al: Antibody to hepatitis B core antigen as a paradoxical marker for non-A, non-B hepatitis agents in donated blood. Ann Intern Med 1986; 104:488-495

2. Stevens CE, Aach RD, Holliger FB, et al: Hepatitis B virus antibody in blood donors and the occurrence of non-A, non-B hepatitis in transfusion recipients. Ann Intern Med 1984; 101:733-738

3. FDA Workshop Examines Benefits/Problems with NANB Hepatitis Surrogate Testing. Council of Community Blood Centers Newsletter. January 23, 1987

## The Achilles Heel of Computer-Initiated Bibliographic Search

To the Editor: The December 1986 special issue on Medical Informatics was timely. Among the uses of Medical Informatics, bibliographic search by computer is widespread.[1] Innovative applications allow the retrieval of more than a list of references.[2,3] For everyone who used to labor for hours through *Index Medicus*, bibliographie searches generated by computers are a welcome convenience. I want to bring to your attention one problem encountered frequently in such searches: The lists of references are incomplete. Incomplete lists are the routine if only two command words are cross-ref-

erenced, for example "edema" and "renal failure," because the references classified under the primary heading "anuria" will be omitted. Even the more sophisticated searches[4] provide incomplete listings more often than one would expect. Unfamiliarity of the searcher with the capabilities of the system or unusual needs of the searcher account without doubt for at least a part of the missing references. But incomplete and nonuniform coding of the articles accounts for a large share of these omissions, I suspect.

A drastic improvement of the bibliographic search will follow a uniform coding. The currently developed Unified Medical Language System[4] will contribute to the improvement of article retrieval. I suggest that active involvement of the editorial staff of medical journals in the process of article classification and coding would be equally important. Currently, many journals do not publish "key" or "index" words. Even journals publishing "index" words provided by the authors do not provide much help because often these index words are not parts of the existing coding system and are not utilized by the coding services. I propose that journals should publish index words and that they should specify in their instructions to authors that only index words conforming to one of the existing classifications, preferably MeSH, will be published. Editorial and reviewing procedures should address this important part of the manuscripts. This process should eliminate, in most instances, the need for changes by the coding services and should give the authors an opportunity to specify their preference for classification of their work.

ANTONIOS H. TZAMALOUKAS, MD
*VA Medical Center*
*2100 Ridgecrest Dr, SE*
*Albuquerque, NM 87108*

REFERENCES

1. Lindberg DAB: Medical information/computers in medicine. JAMA 1986; 256:2120-2121
2. Collen MF, Flagle CD: Full-text medical literature retrieval by computer. JAMA 1985; 254:2768-2774
3. Underhill LH, Bleich HL: Bringing the medical literature to physicians. Self-service computerized bibliographic retrieval. West J Med 1986; 145:853-858
4. Lindberg DAB, Schoolman HM: The National Library of Medicine and Medical Informatics. West J Med 1986; 145:786-790

## Dietary Cholesterol and Atherosclerosis

TO THE EDITOR: After 40 years and probably at least as many millions of dollars spent in the attempt, a direct cause-effect relationship between dietary cholesterol and atherosclerosis has not yet been proved; nevertheless, it has come to be accepted as common knowledge. In her otherwise exemplary, informative and well documented (46 references) article "Diet and Cancer—Should We Change What We Eat?" in the January issue,[1] Susan Desmond, MD, says the following: "coronary artery disease mortality (linked to a high-cholesterol diet). . . ." This is undocumented in the article, and a literature review is not likely to yield significant support.

The basis for this linkage is, as everyone knows, the well-documented decrease in deaths from myocardial infarction in Europe during World War II, when diets were necessarily low in cholesterol. That this concurrence was *not* in fact a cause-effect relationship has been clearly shown by review of autopsy records in Graz, Austria.[2] While deaths from myocardial infarction were reduced by 75% during the war, incidence of atherosclerotic coronary artery disease found at autopsy actually increased. There was a pronounced increase in mortality from infection from 1939 to 1944, with "extra deaths from tuberculosis alone threefold greater than the drop in heart attacks."

Dr Barnes makes a good case for the association of both infectious disease and coronary artery disease with thyroid deficiency,[2] which he calls "the missing link in the genesis of atherosclerosis." By assiduous control of hypothyroidism, relying on basal temperature, in 1,569 cases followed over 8,824 patient-years, he found just four new cases of coronary artery disease.

Dr Barnes' work cannot be said to be controversial since it has been completely ignored, while the myth of high-cholesterol diet/coronary artery disease linkage persists. The findings of a single obscure physician need not be taken at face value, but the reported greater than 90% decrease in incidence of coronary artery disease should be sufficiently provocative to elicit further study.

RALPH S. WOLFSTEIN, MD
*Associate Director*
*Valley Cancer Institute*
*14427 Chase St, #203*
*Panorama City, CA 91402*

REFERENCES

1. Desmond S: Diet and cancer—Should we change what we eat?—Medical Staff Conference, University of California, San Francisco. West J Med 1987; 146:73-78
2. Barnes BO: On the genesis of atherosclerosis. J Am Geriatr Soc 1973; 21:350-354

* * *

### Dr Desmond Responds

TO THE EDITOR: In my article on diet and cancer,[1] I attempted a thorough review of the topic based upon an extensive literature search through many more than the 46 references cited in the article. It is because of this thorough research that I felt qualified to come to conclusions regarding what general dietary guidelines may help to decrease the risk of cancer. Be assured that there has been no direct cause and effect shown between any of these dietary components and cancer. Indeed, it is rare in medicine that one can be dogmatic about proving causality. Nevertheless, as physicians and scientists, we must make causal judgments. To quote A. B. Hill, "All scientific work is incomplete—whether it be observational or experimental. All scientific work is liable to be upset or modified by advancing knowledge. That does not confer upon us a freedom to ignore the knowledge we already have or to postpone the action that it appears to demand at a certain time."[2]

One area of science in which a great deal of advancing knowledge has accumulated recently is that of lipids and atherosclerosis. Dr Wolfstein has questioned whether coronary artery disease can be said to be linked to a high cholesterol diet. As my personal expertise does not extend to this area, I would like to rely on the National Institutes of Health Consensus Conference to reply to this criticism.[3] In December 1984 this group of lipoprotein experts, cardiologists, primary care physicians, epidemiologists, and others met to hear a series of expert presentations and to review all of the available data on lowering blood cholesterol to prevent heart disease. They concluded that "Elevated blood cholesterol is a major cause of coronary artery disease. It has been established beyond a reasonable doubt that lowering definitely elevated blood cholesterol levels will reduce the risk of heart attacks due to coronary heart disease." They also noted, "There is no doubt that appropriate changes in our diet will reduce blood cholesterol levels." These dietary changes include lowering intake of dietary total fat, saturated fat and cholesterol. Clearly, the conclusions of this Consensus Conference would

support the statement that coronary artery disease mortality has been linked to a high-cholesterol diet.

SUSAN D. DESMOND, MD
*Fellow, Hematology-Oncology*
*Cancer Research Institute*
*University of California*
*San Francisco, CA 94143*

#### REFERENCES

1. Desmond S: Diet and cancer—Should we change what we eat?—Medical Staff Conference, University of California, San Francisco. West J Med 1987; 146:73-78

2. Hill AB: The environment and disease: Association or causation? Proc R Soc Med 1965; 58:295-300

3. Lowering Blood Cholesterol to Prevent Heart Disease. Natl Inst Health Consensus Dev Conf Consensus Statement 1985; 5

## The Role of Irradiation

To the Editor: I would like to comment on the article "Subacute Leukoencephalopathy Complicating Acute Lymphoblastic Leukemia" in the February 1987 issue.[1] Cranial irradiation was implicated as a probable cause of the patient's severe delayed leukoencephalopathy. However, in the case presentation, no mention of irradiation was made. We are not told when in the course of the illness the patient received radiation treatment, what area was treated or the total dose and daily fractionation. These factors are all very important in evaluating the contribution of irradiation to the patient's clinical course. Although I do not question the probable role of the irradiation in the patient's illness, I do feel that we in the medical community have a responsibility to discuss radiation effects in objective and specific terms, with reference to the large body of available information.

B. SHARON COLE, MD
*Director*
*Radiation Oncology Department*
*Providence Medical Center*
*500 17th, C-34008*
*Seattle, WA 98124*

#### REFERENCE

1. Filloux FM, Townsend JJ: Subacute leukoencephalopathy complicating acute lymphoblastic leukemia—University of Utah (Clinicopathologic Conference). West J Med 1987 Feb; 146:207-212

* * *

### Drs Filloux and Townsend Respond

To the Editor: Dr Cole is quite justified in inquiring about the details of craniospinal irradiation in this patient, as a single sentence providing this information was inadvertently omitted from the final draft of our manuscript. The patient received 2,360 rads of cranial irradiation in 12 fractions over a three-week period beginning three months after the discovery of malignant cells in the cerebrospinal fluid, and 1,800 rads to the spinal axis in ten fractions during the same period. We regret this serious omission and thank Dr Cole for bringing it to our attention.

FRANCIS M. FILLOUX, MD
*Research Instructor*
*Departments of Neurology, Pediatrics and Psychiatry*
JEANNETTE J. TOWNSEND, MD
*Associate Professor of Pathology and Neurology*
*University of Utah School of Medicine*
*Salt Lake City, UT 84132*

## Incidence of Cough Associated With Captopril Therapy

To the Editor: In an article in the February issue, McNally[1] discusses the incidence and potential pathophysiology of cough occurring in association with captopril therapy. The current labeling for captopril lists cough (along with several other adverse reactions) as occurring "in about 0.5 to 2 percent of patients but did not appear at increased frequency compared to placebo or other treatments used in controlled trials" involving captopril.

The published data cited for the 5% to 15% incidence used by the author are biased by the fact that the frequencies reported describe limited patient groups for whom cough has been a problem—in fact, the author's personal experience would suggest an even higher incidence.

From a data base of approximately 12,000 patients who received captopril in controlled clinical trials, 105 (0.9%) had cough reported as an adverse reaction. The vagaries of the postmarketing experience preclude a reliable frequency determination of any adverse reaction, since both the reaction (numerator) and the population exposed to the drug (denominator) cannot be easily quantified with any degree of accuracy.

Cough occurring in association with angiotensin-converting enzyme inhibitors is a recognized clinical entity,[2,3] albeit poorly understood. The incidence appears to be less than 2% when large groups of patients are reviewed, and individual clinical experiences must be analyzed in this context.

GERALD R. DRESLINSKI, MD
*Associate Director, Clinical Safety*
*ER Squibb & Sons, Inc*
*PO Box 4000*
*Princeton, NJ 08540*

#### REFERENCES

1. McNally EM: Cough due to captopril. West J Med 1987; 146:226-228

2. Webb D, Benjamin N, Collier J, et al: Enalapril-induced cough (Letter). Lancet 1986; 2:1094

3. Inman WHW: Enalapril-induced cough (Letter). Lancet 1986; 2:1218

# Topics in Primary Care Medicine

## Urinary Incontinence

MAJ KURT KROENKE, MC, USA, *and* CAPT G. DOUGLAS CORRIE, MC, USA, *San Antonio, Texas*

*"Topics in Primary Care Medicine" presents articles on common diagnostic or therapeutic problems encountered in primary care practice. Physicians interested in contributing to the series are encouraged to contact the series' editors.*

BERNARD LO, MD
STEPHEN J. McPHEE, MD
Series' Editors

Incontinence is more than just a common illness. Controlled elimination is vital to human dignity. The prevalence of urinary incontinence rises rapidly with age, with the incidence ranging from 5% to 10% among the independent elderly to 30% to 50% among those confined to institutions. Indeed, incontinence is a common reason for nursing home placement.

In the primary care setting, its occurrence and sequelae mandate attention. We shall consider the physiology of normal bladder function and the etiology of, the primary care approach to and the urologic management of urinary incontinence.

### Physiology

Continence requires a proper balance of pressures between the bladder detrusor and the urethral sphincters. The first is the storage tank and pump, the latter the valve and outlet. A relaxed detrusor and contracted sphincters facilitate urine storage. Conversely, when the detrusor contracts and the sphincters relax, urination is initiated. Continence is maintained when urethral pressure equals or exceeds detrusor pressure. Voiding ensues when detrusor pressure exceeds urethral pressure. Any disturbance that increases the detrusor's propulsive forces (bladder pressure) or decreases the sphincter's resistive forces (urethral pressure) promotes incontinence.

Neurologic disorders commonly produce incontinence, with the autonomic system being integral to bladder function. The sympathetic system promotes storage of urine by the dual action of $\alpha$-sympathetic innervation, which stimulates bladder neck (the internal sphincter) contraction, and $\beta$-sympathetic innervation, which inhibits the detrusor muscle. The parasympathetic system initiates voiding by stimulating detrusor contraction. Medications acting on one autonomic pathway may either induce or relieve incontinence. For example, an anticholinergic drug, such as an antihistamine, may weaken detrusor contractions and produce overflow incontinence in a patient whose bladder outlet is already compromised by prostatism. Conversely, the anticholinergic properties of a medication like oxybutynin chloride (Ditropan) are useful when treating the urgency incontinence of detrusor instability.

TABLE 1.—*Characteristics of the Different Types of Neurogenic Bladder*

| | *Site of Neurogenic Lesion* | | | | |
|---|---|---|---|---|---|
| *Bladder Characteristics* | *Cerebrum, Brain Stem* | *Upper Spinal Cord* | *Lower Spinal Cord* | *Sensory Nerve* | *Motor Nerve* |
| Type of incontinence | Detrusor instability | Detrusor instability | Overflow or detrusor instability | Overflow | Overflow |
| Former term | Uninhibited | Reflex | Autonomous | Sensory paralytic | Motor paralytic |
| Voluntary initiation | + | 0 | 0 | + | + |
| Vesical sensation | + | 0 | 0 | 0 | + |
| Bulbocavernous reflex | + | + | 0 | + | 0 |
| Perineal sensation | + | 0 | 0 | + | + |
| Bladder capacity | ↓ | ↓ | ↑ | ↑ | ↑ |
| Residual urine | 0 | 0 | + | + | + |
| Uninhibited contractions | + | + | 0 | 0 | 0 |
| Therapy | Drugs | Drugs | Surgical, ISC | ISC | ISC |

ISC=intermittent self-catheterization, +=present, 0=absent, ↓=decreased, ↑=increased

(Kroenke K, Corrie GD: Urinary incontinence. West J Med 1987 May; 146:623-626)

From the General Medicine Service, Department of Medicine, and the Urology Service, Department of Surgery, Brooke Army Medical Center, Fort Sam Houston, Texas.

The views expressed herein are those of the authors and do not necessarily reflect the views of the United States Army or the US Department of Defense. This article is considered, under the Copyright Revision Act of 1976, a "work of the United States government" and accordingly there is no copyright.

Reprint requests to Kurt Kroenke, MD, Box 523, Beach Pavilion, Fort Sam Houston, TX 78234-6200.

A simplistic approach to neurogenic bladder disorders divides them into those with lesions involving the upper motoneuron (producing a spastic, small-capacity bladder) and those with a lower motoneuron lesion (resulting in a flaccid, large-capacity bladder). The neurogenic control of voiding, however, is more complex than this and is only partly understood. The detrusor has its own intrinsic tone, but this is modulated by sympathetic and parasympathetic input from the sacral part of the spinal cord. Sacral neurons, in turn, are modulated by input from the brain stem and cerebrum, which inhibit simple sacral cord reflexes. The characteristics of a neurogenic bladder depend on the site of the neural lesion (see Table 1). Upper central nervous system lesions, such as stroke, parkinsonism and multiple sclerosis, lead to a loss of voluntary inhibition of bladder contractions, producing detrusor instability and urge incontinence. Lesions of the spinal cord above the sacral neurons, such as multiple sclerosis, transverse myelitis and trauma, likewise produce detrusor instability. In addition, involvement of the ascending and descending tracts may result in an inability to initiate voiding and in a loss of vesical sensation. Lesions of the sacral cord itself—spina bifida, tumor, trauma—can result in hyperreflexia of both the detrusor and the sphincter. An unstable bladder contracts erratically against a hypertonic sphincter. This detrusor-sphincter dyssynergia leads to a high-pressure, poorly emptying bladder. Finally, some lesions may selectively involve the motor (such as poliomyelitis, trauma or congenital anomalies) or the sensory (diabetes, tabes dorsalis) nerves. Such "lower motoneuron" lesions, whether pure motor, pure sensory or mixed, produce an areflexic bladder, which leads ultimately to overdistention and overflow incontinence. The external sphincter is a striated muscle innervated by the pudendal nerve. Although internal sphincter function is more important than the external sphincter in maintaining continence, pudendal nerve damage from trauma or an operation occasionally produces incontinence.

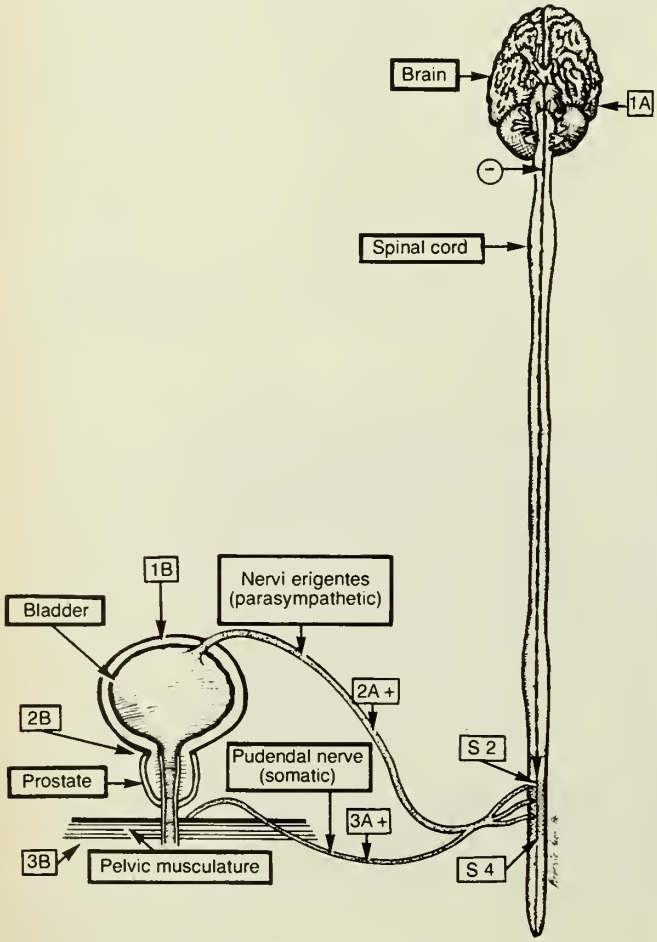



**Figure 1.**—Anatomic localization of urinary incontinence. **(1)** The source of detrusor instability may be an upper motoneuron lesion **(1A)** or intrinsic detrusor instability **(1B). (2)** The cause of overflow can be a lower motoneuron lesion **(2A)** or a bladder outlet obstruction **(2B). (3)** Sphincter incompetence can result from a pudendal nerve lesion **(3A)** or pelvic musculature relaxation **(3B).**

## Etiology

The three major causes of established urinary incontinence—detrusor instability, overflow and sphincter incompetence—are illustrated in Figure 1. Detrusor instability may be caused by a cerebral or an upper spinal cord lesion, by local irritation due to a urinary tract infection or, less commonly, to fecal impaction, a bladder tumor or a distal ureteral stone. It may also be primary—that is, idiopathic—detrusor instability. Detrusor instability may result in urgency incontinence—a sudden urge to void followed by a precipitous loss of urine.

Overflow incontinence may be caused by autonomic neuropathy—diabetes mellitus, sacral cord lesions and so forth—or outlet obstruction, such as prostatic hypertrophy. The bladder progressively distends until intravesical pressure overcomes urethral pressure, resulting in involuntary overflow of urine. The hallmarks of either neurogenic or obstructive overflow incontinence are a distended, palpable bladder and an increased volume of residual urine.

Sphincter incompetence results in stress incontinence, the

TABLE 2.—*Workup for Urinary Incontinence*

*History Elicited*
- Onset—sudden *v* slow
- Pattern—constant *v* occasional
- Urinary symptoms—frequency, nocturia, sensation of postvoiding residual, enuresis
- Volume voided
- Urge present
- Stress-induced—coughing, sneezing, position change
- Medications—anticholinergics, antihypertensives, psychotropics, diuretics and the like
- Past history—parity, menstrual status, pelvic operation, stroke or other neurologic disorder

*Physical Examination Findings*
- Rectal—prostatism, impaction
- Abdominal—palpable bladder
- Pelvic—uterine prolapse, cystocele, atrophic vaginitis
- Neurologic—cortical or spinal cord lesions, peripheral neuropathy, autonomic dysfunction, perineal reflexes and sensation, gait, mental state

*Laboratory Studies*
- Blood chemistry levels—calcium, gulcose, blood urea nitrogen, creatinine
- Urinalysis and urine culture

*Urologic Studies*
- Physiologic measurements
  - Bladder capacity—voided volume plus residual volume
  - Residual urine—100 ml or greater is abnormal
  - Urine flow rate—15 ml/s or less is abnormal
- Special urologic studies—cystometry, voiding cystourethrography, retrograde urethrography, electromyography

voiding of small amounts of urine following maneuvers that increase intra-abdominal pressure, such as coughing, laughing, sneezing or exercising. In multiparous women, weakened muscles of the pelvic floor may allow descent of the bladder neck and upper urethra. This descent can be seen on a cystogram as loss of the urethrovesical angle. Also, as the urethra descends out of the abdominal cavity, increases in intra-abdominal pressure that are normally applied to both bladder and urethra are applied to the bladder alone. Postmenopausal atrophy of the urethral mucosa may contribute to sphincter incompetence but seldom is the sole cause. Operative or traumatic injuries to the pudendal nerve can occasionally produce stress incontinence.

The focus has been on the geriatric population because the prevalence of incontinence rises dramatically with age. Incontinence in younger patients is usually related to anatomic abnormalities (vesicovaginal fistulas, urethroceles), neurologic conditions (multiple sclerosis, spinal cord injuries, congenital anomalies) or sphincter incompetence (multiparity).

## Diagnosis

Primary care physicians need to evaluate patients for transient or reversible causes of incontinence (see Table 2). There are six major transient causes—three *m*'s and three *i*'s: medications, metabolic, mentation changes, infection, impaction and immobility. Although these factors do not normally lead to incontinence, they may precipitate it in a patient with latent dysfunction of the continence mechanism. Medications, a particularly common factor in elderly patients, may disrupt the neurogenic pathways (anticholinergics, antihypertensives and the like), alter mentation (psychotropic drugs) or produce diuresis (diuretics, caffeine, alcohol). Some agents act at several levels. The leading metabolic causes, hyperglycemia and hypercalcemia, induce polyuria and occasionally incontinence. Mental aberrations associated with incontinence include dementia, delirium and depression. Although the first is often irreversible, confusional states and affective disorders should be recognized and treated. Urinary tract infections can result in urgency incontinence. Fecal impactions may produce urgency and outlet obstruction. The impaired mobility of bedridden patients and of persons with gait disturbances can interfere with controlled and independent voiding.

A mnemonic suggested by Resnick that includes basically the same transient causes is DIAPPERS: delirium, infection, atrophic vaginitis, pharmacologic, psychological, endocrine, restricted mobility and stool impaction. The value of either of these mnemonics is that they highlight steps a primary care physician can take before referring a patient for urologic workup.

Incontinence that persists after recognition or exclusion of transient causes deserves further evaluation. History alone can often identify incontinence related to stress (coughing, sneezing or laughing) or urgency (strong, uncontrollable urge to void). If the history suggests stress incontinence, urologic or gynecologic referral is indicated. A physical examination is valuable in detecting a palpable bladder, prostatic enlargement, pelvic pathology and neurologic impairments. The absence of prostatic hypertrophy on a digital examination does not exclude outlet obstruction. Therefore, incontinent men may still require cystoscopy and urine flowmetry to exclude overflow incontinence. The bulbocavernous reflex involves squeezing the glans of the penis or the clitoris while a finger inserted in the rectum feels for anal sphincter contraction. The anal wink consists of anal puckering in response to perineal pinpricks. Absence of these reflexes raises the suspicion of a neurogenic bladder disorder.

Three physiologic measurements—bladder capacity, residual urine and urine flow rate—may be helpful in assessing established incontinence. The first two can be estimated after asking a patient with a full bladder to void. A Foley catheter is then inserted to drain and measure the residual urine. A postvoiding residual volume of less than 100 ml makes retention and overflow incontinence unlikely. The sum of the voided and the residual urine is the bladder's capacity. Bladder capacity has a wide range of normal values. Indeed, an abnormal capacity is determined more by symptoms than by absolute numbers. Nevertheless, the capacity is often considered enlarged when it exceeds 500 to 600 ml and small when it is less than 250 to 300 ml. Urine flow rates are typically measured with a flowmeter. Although a urologist does the

TABLE 3.—*Treatment of Urinary Incontinence*

| *Cause* | *Treatment* |
|---|---|
| *Transient* | |
| Medication | Stop or alter regimen |
| Mental aberrations | Correct cause of delirium; treat depression |
| Metabolic | Hypercalcemia: evaluate and treat; hyperglycemia: hypoglycemic drugs |
| Infection, urinary | Antibiotics |
| Impaction, fecal | Digital removal; enemas |
| Immobility | Assist in transfer and gait; urinal or bedside commode |
| *Established* | |
| Detrusor instability | |
| Upper motor neurogenic (uninhibited; reflex) | Medication: oxybutynin chloride (Ditropan), 5 mg 2 to 4 times a day; imipramine hydrochloride, 25 to 50 mg 1 to 3 times a day; flavoxate hydrochloride (Urispas), 100 to 200 mg 3 times a day |
| Primary (idiopathic) | Bladder training: habit training; biofeedback |
| Overflow | |
| Lower motor neurogenic (areflexic) | Intermittent self-catheterization; habit training; Crede maneuver |
| Outlet obstruction | Surgical treatment (prostatic resection); dilatation (urethral strictures); medication: baclofen, dantrolene sodium (detrusor-sphincter dyssynergia) |
| Sphincter incompetence | |
| Pelvic relaxation (common cause) | Pelvic muscle: (Kegel) exercises—often ineffective; surgical treatment: bladder suspension |
| Atrophic vaginitis (less common cause) | Estrogens—systemic or local |
| Refractory | Diapers, absorbent bed pads; long-term catherization: external condom (men), indwelling (women), suprapubic (men or women) |

measuring, primary physicians should be familiar with the values obtained. Peak flow rates are normally greater than 15 ml per second, whereas flow rates less than 10 ml per second suggest either obstruction or a reduction in detrusor pressure as is seen with an areflexic bladder. Flow rates can vary, however, with the volume voided. By using these physiologic measurements, a patient's bladder dysfunction can often be categorized. Detrusor instability is characterized by a reduced or normal bladder capacity, normal or only slightly reduced flow rates and normal residual volume. Overflow incontinence is associated with an enlarged bladder capacity, diminished flow rates and increased amounts of residual urine.

## Treatment

Therapy is outlined in Table 3. Treatment of transient incontinence is aimed at correcting the underlying cause. Treatment of established incontinence depends on which mechanism is involved. Detrusor instability may respond to drugs such as propantheline bromide that inhibit the cholinergic system, or to drugs that relax the detrusor, such as flavoxate hydrochloride (Urispas). Oxybutynin, possessing both anticholinergic and smooth-muscle-relaxant properties, and imipramine hydrochloride, possessing anticholinergic and $\alpha$-adrenergic properties, are popular choices. Bladder training may also be beneficial and may range from simple habit training using regular toileting times and symptom diaries to various biofeedback methods using cystometry, electromyography or anal balloons.

Overflow incontinence due to outlet obstruction generally requires invasive intervention such as resection of a hypertrophied prostate or dilatation of a urethral stricture. Functional outlet obstruction caused by detrusor-sphincter dyssynergy may respond to the administration of baclofen or dantrolene sodium. Overflow related to neurogenic causes is more difficult to treat. It is easier to inhibit an unstable detrusor than to stimulate a hypotonic one. Whereas anticholinergic medications and smooth-muscle relaxants can be used with some success in detrusor instability, cholinergic drugs are disappointing in the treatment of weak detrusor contractions. The role of bethanechol chloride (Urecholine) is controversial. Although frequently used, convincing evidence supporting its efficacy is lacking. Because pharmacotherapy is generally inadequate, neurogenic overflow incontinence often requires intermittent self-catheterization. Habit training as well as external pressure applied over the suprapubic area (the Crede maneuver) may also be useful.

Stress incontinence associated with atrophic urethral tissue may respond to estrogen therapy. If the incompetent sphincter is due primarily to muscular weakening, pelvic muscle strengthening (Kegel) exercises are sometimes effective, although surgical intervention is usually required. The traditional Marshall-Marchetti-Krantz cystourethropexy and the transvaginal bladder suspension may both reduce stress-related leakage.

It is important to realize that detrusor instability may coexist with other established causes of incontinence. Therefore, a woman undergoing surgical treatment for stress urinary incontinence and a man undergoing transurethral resection of the prostate for outlet obstruction may have residual urgency incontinence if detrusor instability is still present postoperatively. Likewise, an elderly man given empiric medication for detrusor instability might also have latent outlet obstruction and urinary retention may develop.

Refractory incontinence may lead to a need for ongoing indwelling catheterization in women, for external condom catheters in men or for diapers and absorbent bed pads in either. A typical person requiring such measures might be an elderly, bedridden patient with dementia in whom a comprehensive workup either is not feasible or has failed to disclose a treatable cause. The development of bacteriuria is inevitable with long-term catherization, but antibiotics should be reserved for symptomatic infections to avoid selection of resistant organisms. With the use of diapers and bed pads, meticulous attention to skin care is important to avoid serious decubital ulcers.

### GENERAL REFERENCES

Finkbeiner AE: Is bethanechol chloride clinically effective in promoting bladder emptying? A literature review. J Urol 1985; 134:443-449

Hadley EC: Bladder training and related therapies for urinary incontinence in older people. JAMA 1986; 256:372-379

Kendall AR, Karafan L: Classification of neurogenic bladder disease. Urol Clin North Am 1974; 1:37-44

Ouslander JG: Urinary incontinence in the elderly. West J Med 1981; 135:482-491

Resnick NM, Yalla SV: Management of urinary incontinence in the elderly. N Engl J Med 1985; 313:800-805

Rowe JW, Resnick NM: Disorders of the kidney and urinary tract, chap 47, *In* Andres R, Bierman EL, Hazzard WR (Eds): Principles of Geriatric Medicine. New York, McGraw-Hill, 1985, pp 623-627

Williams ME, Pannill FC: Urinary incontinence in the elderly: Physiology, pathophysiology, diagnosis and management. Ann Intern Med 1982; 97:895-907

# Survival Following Cardiac Transplantation—What Are Acceptable Standards?

DALE G. RENLUND, MD; MICHAEL R. BRISTOW, MD, PhD; NELSON A. BURTON, MD; KENT W. JONES, MD; S. V. KARWANDE, MD, *and* WILLIAM A. GAY, Jr, MD, *Salt Lake City*

*In an 18-month period, 50 orthotopic cardiac transplantations were done in Utah in 48 patients with end-stage heart failure. The 12-month actuarial survival was 98%, indicating that successful cardiac transplantation can be done in a newly established program and that the intermountain West has an adequate supply of potential recipients and donors for a moderate- to high-volume program. Furthermore, the administration of cardiac transplantation in a setting of other treatment modalities of heart failure in a multi-institutional program that crosses private practice-academic barriers is feasible. Results such as these need to be considered by the federal government as it establishes eligibility criteria for centers to be approved for Medicare-funded cardiac transplantation.*

(Renlund DG, Bristow MR, Burton NA, et al: Survival following cardiac transplantation—What are acceptable standards? West J Med 1987 May; 146:627-630)

Cardiac transplantation remains a costly, labor-intensive and complicated treatment for end-stage cardiac dysfunction.[1] During 1985 the number of institutions in the United States doing cardiac transplantation increased from 37 to 74 and the number of these procedures increased nearly fivefold.[2] It is generally held that successful cardiac transplant programs must have a reasonable volume of patients, necessitating their location in a large metropolitan area; have been established for some period of time so that the "learning curve" is passed; be administered consistently so that only one hospital in a multi-institutional program does the procedure, and be separated from other treatment modalities of end-stage heart failure. Inasmuch as the federal government is presently considering several of these criteria in determining which centers will be eligible for Medicare funding of cardiac transplantation,[3] a consideration of their relative importance is timely.

Ostensibly the government's involvement relates to the notion that cardiac transplantation requires a scarce resource, the health-care dollar, and that regulation of its expenditure is appropriate.[4] Focus on the financial concerns, however, may ignore important ethical considerations. The limiting resource in cardiac transplantation is the availability of donor organs. When a significantly higher success rate is achieved in some institutions than in others, transplantation at the inferior institutions represents wastage of a resource that is in extremely scarce supply. The success rate in transplantation also affects cost, as the treatment of complications carries an increased output of health care dollars and loss of potential productivity. Therefore, it seems desirable that strict criteria for success in cardiac transplantation be used by any regulatory body attempting to allocate scarce resources of all types.

With the first cardiac transplantation done in the state of Utah 18 months ago,[5] the testing of the following assertions began: that successful results could be obtained without a lengthy "learning curve" if sufficient preparation and expertise were assured; that there existed a large volume of eligible recipients and donors in the intermountain West; that a consistent program could be administered in three institutions, blending academic and private practice interests and enabling the use of more resources than any single institution could afford, and that it is advantageous to do cardiac transplantation in a setting of other treatment modalities of heart failure. Our initial experience challenges some of the previously held notions about cardiac transplantation and suggests that the standard of success in cardiac transplantation should be higher than is generally considered acceptable.

## Methods

### *Hospitals*

The three hospitals used for the cardiac transplantations in Utah are in the University of Utah's teaching hospital system. They consist of LDS Hospital, a 520-bed private facility; the University of Utah Hospital, a 400-bed patient care facility on the campus of the University of Utah, and the Veterans Administration Medical Center (VAMC), a 367-bed patient care hospital. All three hospitals are modern, tertiary referral hospitals drawing patients from the entire intermountain West. Their respective referral systems encompass the vast majority of patients in Utah, southern and eastern Idaho, central and

From the UTAH Cardiac Transplant Program, Division of Cardiology, University of Utah School of Medicine Medical Center, the Veterans Administration Medical Center and the LDS Hospital, Salt Lake City. The personnel of the Utah transplant-affiliated-hospitals Cardiac Transplant Program—*Cardiovascular Surgeons:* Nelson A. Burton, MD; Donald B. Doty, MD; William A. Gay, Jr, MD, (Surgical Director); Kent W. Jones, MD; S. V. Karwande, MD; *Cardiologists:* Jeffrey L. Anderson, MD; Michael R. Bristow, MD, PhD, (Medical Director); J. Lee Burke, MD; Clement C. Eiswirth, MD; Edward M. Gilbert, MD; Donald L. Lappe, MD; Jeffrey A. Laser, MD; John B. O'Connell, MD; Dale G. Renlund, MD; Theophilos J. Tsagaris, MD; Sherman G. Sorensen, MD; Richard B. Sutton, MD; *Transplant Coordinators:* Jan Curtis, RN; Linda A. Freedman, RN; Colette M. Herrick, RN, (Chief Coordinator); Patrice C. Mealey, RN; Cherylyn Robinson, RN; *Transplant Surgical Coordinator:* William Wong, PA; *Pathologists:* Thomas V. Colby, MD; M. Elizabeth Hammond, MD; Randall G. Lee, MD.

Reprint requests to Dale G. Renlund, MD, Division of Cardiology, University of Utah Medical Center, 50 N Medical Dr, Salt Lake City, UT 84132.

ABBREVIATIONS USED IN TEXT

ATG = antithymocyte globulin
IV = intravenously
PVR = pulmonary vascular resistance
VAMC = Veterans Administration Medical Center

eastern Nevada, southern and western Wyoming and southeast Montana.

*Administration*

Overall direction of the program is provided through an executive committee consisting of a medical director, a surgical director and representatives from each hospital (see Figure 1). This executive committee is composed of University of Utah faculty along with private cardiac surgeons and cardiologists at LDS Hospital. The goals of the program were to establish a clinical and basic research program dedicated to solving problems in transplantation and investigating mechanisms responsible for heart muscle disease and heart failure, and to provide a clinical service to patients in the intermountain West. The executive committee meets at least weekly to ensure progress towards these goals. It reviews and prioritizes cases, is updated on the clinical course of inpatients and outpatients with transplants, addresses concerns from each hospital and ensures consistency in patient care at each participating hospital.

Heart failure clinics were established for the three institutions. In these settings, the most appropriate of many treatment modalities could be selected for individual patients, ranging from conventional medical treatment, referral for revascularization or surgical intervention other than cardiac transplantation, investigational medications or cardiac transplantation. Patients who met the following criteria were considered for transplantation.

- Severe, New York Heart Association class IV cardiac dysfunction unremedial to surgical treatment other than cardiac replacement.
- Limited life expectancy, with a one-year survival estimated to be less than 50%.
- Age younger than 65 years.
- No systemic illness other than abnormalities related to heart failure.
- Emotional stability.
- The presence of an adequate psychosocial support system.
- Absence of the following:
  1. Pulmonary hypertension (pulmonary vascular resistance [PVR] more than 8 Wood units or a PVR of more than 6 Wood units with inability of sodium nitroprusside infusion to reduce the PVR to below 3 Wood units or inability to reduce pulmonary artery systolic pressure below 50 mm of mercury).
  2. Severe irreversible hepatic, renal or pulmonary disease.
  3. Active systemic or pulmonary infection.
  4. Recent pulmonary infarction.
  5. Diabetes mellitus requiring insulin.
  6. History of uncontrollable hypertension.
  7. Systemic vascular or cerebrovascular disease.
  8. Active peptic ulcer disease.
  9. Unresolved substance abuse.

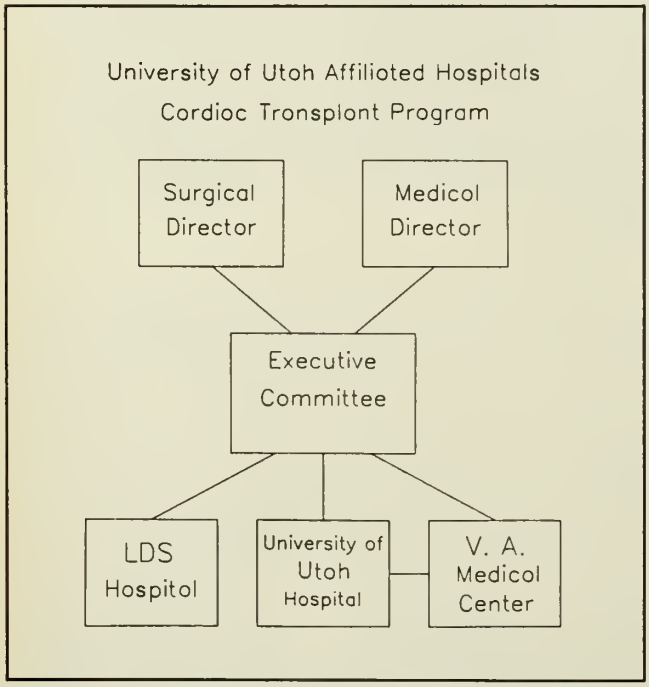



**Figure 1.**—Administrative structure of Utah Transplant Affiliated Hospitals Cardiac Transplant Program. The program is directed by an executive committee composed of the officers indicated above.

Preoperative and postoperative medical care including immunosuppressive therapy and posthospital discharge care and surveillance are provided by the transplant medical team using the heart failure clinic as a base for all outpatient work. Graft placement and organ harvest are done by a five-member cardiovascular surgery team consisting of two LDS Hospital surgeons, two Utah University Hospital surgeons and one VAMC surgeon. Donors are screened by a member of the executive committee once potential donor brain death has been declared. Laboratory data that are routinely acquired include hepatitis screening, human immunodeficiency virus screening, chest x-ray film, arterial blood gas determinations and electrocardiogram. An echocardiogram is additionally done[6] if possible. Also, the time, date and type of accident are ascertained along with the types of injuries sustained. Before approval for use as a donor, the current medications, in particular vasopressors, with their dosage and duration of treatment are determined. Diabetes insipidus is treated and blood pressure, heart rate and volume state are optimized.

*Immunosuppression*

During the 18-month period, three immunosuppressive protocols were used, dictated primarily on the basis of the supply of equine antithymocyte globulin (ATG) (Atgam, Upjohn Pharmaceutical Company):

Protocol 1. The use of ATG without steroid pulse
Protocol 2. The use of ATG with steroid pulse
Protocol 3. The use of OK T3 monoclonal antibody with steroid pulse.

In both protocols 1 and 2, patients preoperatively received cyclosporine, 3 mg per kg body weight given intravenously (IV); ATG, 10 mg per kg IV, and azathioprine sodium, 4 mg per kg IV. Intraoperatively, methylprednisolone sodium succinate, 500 mg, was administered. Postoperatively, patients received methylprednisolone, 125 mg IV every eight hours for three doses; azathioprine, 2 mg per kg given IV or orally

per day; ATG, 10 mg per kg given IV daily for seven days; cyclosporine, 2 mg per kg IV on postoperative day 1 and then 12 mg per kg per day given orally in two divided doses beginning on day 2. The cyclosporine dose was then adjusted to maintain a level of 200 to 300 ng per ml for 30 days and then further adjusted to maintain a level of 75 to 200 ng per ml thereafter.

Protocol 2 differed from protocol 1 in that on day 8, prednisone, 1 mg per kg, was administered daily for seven days and then tapered over two weeks.

Protocol 3 differed in that preoperatively only azathioprine, 4 mg per kg given IV, was used. Methylprednisolone was administered intraoperatively at the same dose of 500 mg. Postoperatively, methylprednisolone, 125 mg, was administered every eight hours for three doses and then 5 mg OK T3 was given IV daily for 14 days. Azathioprine was administered daily at 2 mg per kg postoperatively. Cyclosporine was first begun on day 4 at a dose of 6 mg per kg per day orally in two divided doses and adjusted to a serum concentration of 100 to 200 ng per ml. On day 15, prednisone, 1 mg per kg, was given in two divided doses for seven additional days and then tapered over two weeks.

Since patient 8, all patients have been randomly selected to receive vincristine sulfate, 0.025 mg per kg for eight doses, or no vincristine (beginning on day 9 for protocols 1 and 2 and day 17 for protocol 3).

A biopsy was taken weekly for six to eight weeks and then the frequency of biopsies was decreased depending on the state of cardiac rejection. For treatment of rejection, high-dose methylprednisolone therapy was used, with or without ATG, OK T3 or rabbit antilymphocyte globulin, followed by tapering doses of prednisone. Following the prophylactic use of prednisone, as in protocols 2 and 3, or after its use in the treament of rejection, the prednisone dosage was tapered and discontinued unless cardiac rejection recurred. This tapering and discontinuing, if possible, was attempted repeatedly until three rejection episodes had occurred in a particular patient, at which point the prednisone dosage was subsequently tapered to a low maintenance dose.

## Results

From March 8, 1985, to September 7, 1986, we evaluated 153 patients in the combined heart failure clinics. Three underwent other surgical procedures (one revascularization, two a valvular operation), 67 were assigned to experimental therapy, 35 were directly assigned to cardiac transplantation with conventional therapy until the time of transplantation and 48 were treated conventionally without being assigned to transplantation. Of the patients assigned to experimental therapy, 19 were subsequently assigned to cardiac transplantation. In the initial evaluation of three of these patients, it had been felt that they had inadequate emotional stability or insufficient family support to undergo transplantation. After observing them for the duration of the particular investigational study, however, the initial evaluation was found to be in error. This would likely not have been noted without the follow-up afforded by an investigational study. Of those in whom conventional therapy was used, none were subsequently assigned to transplantation.

Table 1 shows the age, sex, cause of heart failure, average number of previous heart operations, pretransplant ejection fraction and the number requiring pretransplant hemodynamic support in 48 patients who underwent cardiac trans-

TABLE 1.—*Heart Transplant Patient Characteristics in 48 Patients*

| *Patient Characteristics* | *Values* |
|---|---|
| Age, years | 45.0±12.4* |
| Median | 48 |
| >50 years old, % | 44 |
| Range | 16 to 63 |
| Sex | |
| Male, No. (%) | 43 (89.5) |
| Female, No. (%) | 5 (10.5) |
| Cause of heart failure, No. (%) | |
| Idiopathic dilated cardiomyopathy | 25 (52.1) |
| Coronary artery disease-induced cardiomyopathy | 19 (39.5) |
| Valvular heart disease-induced cardiomyopathy | 2 ( 4.2) |
| Hypertrophic cardiomyopathy | 1 ( 2.1) |
| Acute myocarditis | 1 ( 2.1) |
| Previous chest operation, No. | 0.5±0.77* |
| Range | 0 to 3 |
| Pretransplant ejection fraction | 0.18±0.05*† |
| Range | 0.10 to 0.27*† |
| Pretransplant hemodynamic support | |
| Inotropic agents (other than digoxin)‡ | 18 |
| Intra-aortic balloon counterpulsation | 4 |

*Mean ± standard deviation.
†Does not include a patient with hypertrophic cardiomyopathy whose ejection fraction was greater than 70%.
‡Inotropic agents: dopamine, dobutamine, enoximone, norepinephrine (levarterenol) bitartrate.

TABLE 2.—*Transplant Recipients' State of Residence*

| *State* | *Number* | *Percent* |
|---|---|---|
| Utah | 16 | 33 |
| Nevada | 8 | 17 |
| Idaho | 8 | 17 |
| Montana | 6 | 12 |
| Wyoming | 4 | 8 |
| Alaska | 3 | 6 |
| Oregon | 1 | 2 |
| Oklahoma | 1 | 2 |
| Missouri | 1 | 2 |

TABLE 3.—*Distribution and Survival of Cardiac Transplant Recipients Among the Utah Transplant Affiliated Hospitals*

| *Category* | *UUH* | *LDSH* | *VAMC* | *Total* |
|---|---|---|---|---|
| Transplants | 24 | 14 | 12 | 50 |
| Patients | 23 | 13 | 12 | 48 |
| Survivors | 22 | 13 | 12 | 47 |
| 12-Month actuarial survival, % | 96 | 100 | 100 | 98 |

LDSH=LDS Hospital, UUH=University of Utah Medical Center, VAMC=Salt Lake City Veterans Administration Medical Center

TABLE 4.—*Transplant Recipient Distribution Among Immunosuppressive Protocols and Incidence of Serious Infection*

| | | *Serious Infections* | |
|---|---|---|---|
| *Protocol** | *Total Enrolled* | *Number* | *Percent* |
| 1 | 16 | 4 | 25 |
| 2 | 17 | 6 | 35 |
| 3 | 15 | 4 | 27 |

*Protocol 1: equine antithymocyte globulin (ATG) given without steroid pulse; protocol 2: ATG given with steroid pulse; protocol 3: OK T3 given with steroid pulse.

plantation. It seems that this patient group does not represent a select group of young, healthy patients in whom survival would be expected to be higher. This is supported by the finding that 18 patients were hemodynamically supported preoperatively (4 with intra-aortic balloon pump and inotropic agents, 14 with inotropic agents alone).

Table 2 shows the state of residence of the patients who received transplants. Although 33% are from Utah, other intermountain states are well represented.

During this time period, of the 54 assigned to transplantation, 50 transplants were done in 48 persons (see Table 3). Two patients required retransplantation due to refractory rejection and hemodynamic compromise. There were six deaths in the transplant waiting list, and 1 of the 48 transplant patients succumbed to rejection. This patient died on day 9 of protocol 1. The 12-month actuarial survival is 98% in those transplanted—with an average follow-up of $8 \pm 6$ months and a range of 0.5 to 18 months—and 87% in those approved for transplantation.

Table 4 shows the number of patients enrolled in each protocol and the number of serious infections in each group. There is no difference in the three protocols with regard to serious infections. These infections were cytomegalovirus pneumonitis (one), *Pneumocystis carinii* pneumonia (two), *Legionella* pneumonia (two), *Staphylococcus epidermidis* pneumonia (two), pneumococcal pneumonia (three), *Pseudomonas* bronchiolitis (one), *Staphylococcus aureus* pulmonary abscess (two), *S aureus* mediastinitis (two), abdominal wound *Pseudomonas* (one) and *Pseudomonas* urinary tract infection (one).

In the 42 patients who are presently on maintenance immunosuppressive regimens, 20 (48%) have had their steroid therapy successfully tapered off. Overall, there have been 66 episodes of moderate rejection (defined as the presence of interstitial lymphocytic infiltrates with or without necrosis) or of greater severity. Protocol 3 has clearly been associated with less rejection. Complete discussions of the immunosuppression results are presented elsewhere.[7,8]

## Discussion

The results indicate that excellent survival can be achieved in a new cardiac transplantation program. This is possible because the science and art of transplantation have been elucidated in well-established programs such as that at Stanford University.[9] To accept a high mortality rate in new programs, simply because they are new, seems inappropriate. In fact, the Medicare-proposed one-year minimal actuarial survival of 70% appears intolerably low for any program.

Our experience also shows that successful transplantation need not be carried out in a large metropolitan area. It is also clear that volume need not be high in individual hospitals to achieve excellent results if the team caring for patients has experience with a relatively large population. The total volume of cases in the Utah program was high from the beginning, reflecting a relatively large referral base and an adequate donor supply in the intermountain West.

It is doubtful whether any individual hospital in the group could have carried out 50 transplants in the past 18 months. It was in an effort to consolidate resources and minimize competition for donor hearts that the three-hospital approach was undertaken.[5] Because a common medical team cares for patients in all hospitals, patient care is uniform. Private practitioners and academic faculty interests have been able to combine in this effort to obtain the present results.

Clearly it is not detrimental to administratively incorporate clinical cardiac transplantation in a setting that deals with all treatment modalities for heart failure. In fact, our experience suggests that this may be the best approach. Cardiologists, nurse coordinators and ancillary staff are thereby well acquainted with the patients before transplantation, and the patients are well acquainted with them. Medication compliance, emotional stability and family support systems can be extensively evaluated during nontransplant therapy. Patients in whom cardiac dysfunction is not severe enough to be considered for transplantation can be prospectively observed carefully for signs of deterioration.

Given our experience and the experience of certain other recently established programs,[10] it would seem that a survival rate of less than 80% in 12 months of any program is unacceptable. Furthermore, given the constraints that exist in donor supply, if the survival rate in a well-established program does not approach 90%, reasons for this excessively high mortality should be sought, identified and corrected. It can be argued that to do this procedure with a lesser standard is unethical, as a precious and limited commodity (donor hearts) is wasted by such results.

In summary, high mortality is not intrinsic to new cardiac transplant programs and should be unacceptable in any cardiac transplant program. The intermountain West has an adequate supply of potential recipients and donors for a cardiac transplant program with a moderate to high volume. A multiinstitutional program that crosses private practice-academic barriers is feasible. Finally, cardiac transplantation complies rationally and optimally with heart failure research goals, and the combination of these two programs under one administrative unit likely enhances the outcome of each.

### REFERENCES

1. Evans RW: The socioeconomics of organ tranplantation. Transplant Proc 1985; 17:129-136

2. Iterim Report—Transplantation Summary, Office of Health Technology Assessment, December 1985. Government Printing Office, 1986

3. Organ Transplantation, Issues and Recommendations—Report of the Task Force on Organ Transplantation. US Department of Health and Human Services, Public Health Service, Health Resources and Services Administration, Office of Organ Transplantation, April 1986

4. Evans RW: The heart transplant dilemma. Issues Sci Technol 1986 Spring, pp 92-101

5. Burton NA, Gay WA Jr, Jones KW, et al: Heart transplantation in Utah: Results in a multiinstitution program. J Heart Transplant 1986; 5:69-70

6. Gilbert EM, Sorensen S, Laser J, et al: Echocardiography as the primary means of screening cardiac transplant donors. Circulation 1986; 74 (Suppl II):178

7. Gilbert EM, Eiswirth CC, Renlund DG, et al: Use of OKT3 monoclonal antibody in cardiac transplantation: Early experience with rejection prophylaxis and treatment of refractory rejection. Transplant Proc, in press

8. Gilbert EM, DeWitt CW, Eiswirth CC, et al: Treatment of refractory cardiac allograft rejection with OKT3 monoclonal antibody. Am J Med 1987; 82:202-206

9. Fowler MB, Schroeder JS: Current status of cardiac transplantation. Mod Concepts Cardiovasc Dis 1986; 55:37-41

10. Transplantation Around the World Section. J Heart Transplant 1986; 5:46-87

Public Health and Preventive Medicine

# Preventive Dentistry Update—Dental Sealants

ROBERT ISMAN, DDS, MPH, *and* KENNETH W. KIZER, MD, MPH, *Sacramento, California*

Today's physician has an opportunity to help promote a technology that promises to revolutionize preventive dentistry. The time is at hand for virtually eliminating tooth decay, and new generations can look forward to a life free from the pain, discomfort, time lost from work and school and cost associated with the progression and treatment of this disease.

The prevalence of dental caries has declined dramatically in the United States over the past decade. Among 5- to 17-year-old children, the prevalence of caries declined by 32% between 1971-1973 and 1979-1980, and 37% of these children had never had caries.[1] The reasons for this decline are not known with certainty, but most observers believe it is attributable to the increased use of fluoride, especially fluoride-containing dentifrices.

At the same time caries prevalence has declined, there has also been a change in the pattern of caries attack. The 1979-1980 National Dental Caries Prevalence Survey found that 84% of the caries occurred on the pit and fissure surfaces of the teeth. A recent evaluation of a school-based preventive dental program in California found that more than 90% of the caries in children in grades kindergarten through sixth was on these surfaces, and less than 10% was on smooth surfaces.[2]

It has long been known that fluoride disproportionately benefits the smooth surfaces of teeth. It appears that the use of fluorides has contributed greatly to the overall decline in caries prevalence, and that most caries now occurs on those tooth surfaces least likely to benefit from fluorides. Thus, the current pattern of caries prevalence favors a preventive technology that would protect the pit and fissure (primarily chewing) surfaces of the teeth. Such a technology currently exists. Pit and fissure sealants have been shown to dramatically reduce the incidence of pit and fissure caries. The combined use of fluorides and sealants means that, for the first time in history, the possibility theoretically exists for eliminating caries.

## How Do Sealants Work?

Sealants are acrylic-like materials that are applied to prepared tooth surfaces much as fingernail polish is applied and are then hardened by a chemically or light-induced polymerization process.

The pit and fissure surfaces of the teeth are especially prone to decay because bacteria lodge in them and are nourished by food products in the mouth, thus initiating the acid-producing process that leads to decay. The pits and fissures are too small and deep to be reached by even the smallest of toothbrush bristles and so are usually the first surfaces to decay. Sealants form a physical bond with the tooth enamel and cover the pit and fissure surfaces, resulting in a smooth surface that can easily be kept clean by toothbrushing.

The process of sealing a tooth begins by first cleaning the tooth. The tooth is then etched with a dilute solution of phosphoric acid, which removes about 10 microns of enamel and makes the enamel more porous, thus allowing the sealant material to flow into the porous enamel and bond physically with it. The tooth is then dried, the sealant is applied and then polymerized. It usually takes 15 to 20 minutes per patient for a dental professional to seal as many as four teeth at a time.

When sealants first began being used, there was concern about sealing over undetected areas of decay and allowing the decay process to progress unretarded. In fact, research has shown that just the opposite occurs.[3] When a tooth is sealed, virtually all bacteria beneath the sealant are killed because they are deprived of the air and food they need to survive and multiply. In fact, some preliminary studies suggest that sealants might be used to seal over some areas of active decay and actually stop the decay process.

Because the decay process can begin as soon as a tooth erupts, sealants should be applied as soon after tooth eruption as possible. In private dental practice settings, sealants are usually applied to recently erupted teeth with well-developed pits and fissures and in persons with previous caries experience because if there is no decay present, sealants may not be indicated. Permanent molars and bicuspids are the teeth most likely to be sealed because they are the most prone to decay and have the anatomic features most conducive to sealant retention.

In public settings such as schools, sealants are often applied only to molars because this is where most decay occurs. The evidence to support the effectiveness of sealing primary teeth is less conclusive than that for permanent teeth.

The first and second permanent molars are the most susceptible to decay and generally erupt at about ages 6 and 12 years, respectively. Physicians can play an important role in bringing the benefits of sealants to their patients near these ages because children are more likely to see a physician regularly than a dentist. By being aware of the approximate eruption times of susceptible teeth (Table 1), physicians can alert parents to the availability and benefits of sealants. There is some evidence that patient demand has contributed to the increasing number of dentists who are providing sealants as a routine preventive service.[4]

(Isman R, Kizer KW: Preventive dentistry update—Dental sealants. West J Med 1987 May; 146:631-632)

From the Office of Dental Health, California Department of Health Services, Sacramento.

Reprint requests to Robert Isman, DDS, MPH, Chief, Office of Dental Health, California Department of Health Services, 714 P St, Room 440, Sacramento, CA 95814.

TABLE 1.—*Approximate Median Age of Tooth Eruption for Permanent Teeth Most Likely to Benefit From Sealants**

| Permanent Tooth | Approximate Median Age at Eruption, Years |
|---|---|
| Lower first molar | 6.0 |
| Upper first molar | 6.1 |
| Lower first bicuspid | 10.2 |
| Upper first bicuspid | 10.3 |
| Lower second bicuspid | 10.8 |
| Upper second bicuspid | 11.2 |
| Lower second molar | 11.4 |
| Upper second molar | 12.0 |

*Source: US Department of Health and Human Services, National Institute of Dental Research: Effective Age of Tooth Eruption, 1979-80—Data From the National Dental Caries Prevalence Survey (Janet A. Brunelle, MS, Chief, Biometry Section, NIDR, written communication, June 1985).

## Effectiveness of Sealants

Research has shown that if the sealant is retained on the tooth, the tooth will not decay.[5] Results with early sealant materials, first developed 15 to 20 years ago, were not very promising—that is, the sealants were not retained very long. Today's sealants are far superior to the early ones. Some studies have shown retention rates of more than 80% after five years.[6] More recent studies show that sealants are still retained after ten years, with significantly less decay in the sealed teeth. The importance of this is that for most people, if the sealant can be retained during the most caries-prone years—that is, adolescence—the risk of caries in older age groups is substantially lower.

The most important factor in determining the effectiveness of sealants is keeping the tooth dry during sealant application. Contamination with saliva, even for only a second or two, has been shown to reduce sealant effectiveness dramatically. One variable that is not a factor in effectiveness is who applies the sealant. Studies have shown that dental auxiliary personnel (dental hygienists and dental assistants) can apply sealants just as effectively as dentists.[7]

## Alternatives and Costs

Studies of cost-effectiveness must necessarily ask the question, "compared with what?" Most cost-effectiveness studies of sealants have compared them with silver amalgam fillings—the most common restorative material used in dentistry. The usual assumption is that amalgams are permanent restoration—that is, that they last a lifetime. But the evidence does not support this notion. Two studies showed that 50% of all amalgams were replaced after five to ten years.[8,9] Another rated only 16% of amalgams as "acceptable" after ten years.[10] Another found that a third of dentists' time was spent replacing defective amalgams.[11] Therefore, it is probably not realistic to think of amalgams as permanent restorations when comparing them with sealants.

Another issue to examine when considering the question of cost-effectiveness is the appropriateness of comparing a preventive procedure (sealants) with a restorative one (amalgam). Fluorides have basically acted to keep decay at a controllable level. The combined use of both fluorides and sealants could virtually end decay. Society needs to ask if sealants are worth the marginal cost. In other words, do we say that caries is under sufficient control now and that to eliminate the caries that is left by using sealants will cost too much? If the value placed on the virtual elimination of decay becomes high enough, sealants will be viewed as cost-effective.

The average fee for sealants in private practice was about $11 per tooth in 1982, according to a fee survey by the American Dental Association.[12] This represented about half the fee for a simple amalgam filling. A number of state and local health departments also conduct sealant programs, usually in school settings. In such settings, the costs have averaged about $7 to $8 per child, or $1.60 per tooth sealed.[13] Data from a state health department-sponsored sealant program in New Mexico indicate that the program not only saved 75% of the teeth that otherwise would have decayed, but also reduced the repair and treatment costs by 55% (James J. Calderone, DDS, DrPH, Chief, Preventive Health Services Bureau, New Mexico Health and Environment Department, oral communication, August 1985).

## Conclusions

Dental sealants represent a technology that has been shown to be safe, highly effective and less costly than restorative dental procedures. In addition, sealants provide a pleasant introduction to dental care, are more esthetic than many restorative materials and can enhance a person's sense of self-esteem at having a mouth free of caries.

Sealants are easily applied and are applied effectively by all members of a dental health team. Using dental auxiliaries to apply sealants offers the potential to lower the costs of the procedure particularly in public programs.

Sealants are currently underused in both private dental offices and public dental programs. Physicians have an opportunity to help increase their use in both settings.

Sealants are the most exciting advance in preventive dentistry since the introduction of fluorides. Physicians can help assure the increased use of sealants by being aware of the procedure, encouraging their use in public dental programs and encouraging their patients to request the procedure from their dentists.

### REFERENCES

1. The Prevalence of Dental Caries in United States Children 1979-80—The National Dental Caries Prevalence Survey. US Department of Health and Human Services, National Institute of Dental Research, 1981, pp 1-8

2. Silverstein SJ, Pollick HF, Fine JI: Evaluation of the state of California children's dental disease prevention program. San Francisco, University of California School of Dentistry, 1984, p 3

3. Going RE: Sealant effect on incipient caries, enamel maturation, and future caries susceptibility. J Dent Educ 1984 Feb; 48:35-41

4. Cohen L, LaBelle A, Romberg E: Strategies for Increasing the Use of Pit and Fissure Sealants in Dental Practice. Baltimore, Baltimore College of Dental Surgery, 1985, pp 63-64

5. Ripa LW: Occlusal sealants: An overview of clinical studies. J Public Health Dent 1983 Summer; 43:216-225

6. Simonsen RJ: Five-year results of sealant effects on caries prevalence and treatment cost. J Dent Res 1982; 61:332

7. Leske GS, Pollard S, Cons N: The effectiveness of dental hygienist teams in applying a pit and fissure sealant. J Prevent Dent 1976; 3:33-36

8. Robinson AD: The life of a filling. Br Dent J 1971; 130:206-208

9. Allan DN: A longitudinal study of dental restorations. Br Dent J 1977; 143:87-89

10. Hamilton JC, Moffa JP, Ellison JA: Ten-year clinical evaluation of two different amalgams. J Dent Res (Special Issue A) 1981; 60:521

11. Moore DL, Stewart JL: Prevalence of defective dental restorations. J Prosthet Dent 1967; 17:372-378

12. Bureau of Economic and Behavioral Research: Dental fees charged by general practitioners and selected specialists in the United States, 1982. J Am Dent Assoc 1984; 108:83-87

13. Calderone JJ, Mueller LA: The cost of sealant application in a state dental disease prevention program. J Public Health Dent 1983 Summer; 43:249-254

# Medical Ethics

## Consultations in Clinical Ethics—Issues and Questions in 27 Cases

JOHN LA PUMA, MD *Chicago*

Hospital consultations in clinical ethics are a new development in patient care. Physicians often have faced and resolved problems in clinical ethics—moral problems in the care of a particular patient—on their own. Few physicians have been trained or available to help solve clinical ethical problems in the hospital.

To clarify ethical problems and to teach methods of ethical analysis, a movement toward providing ethics consultations in the hospital has grown in the past several years.[1-5] The consultative function of hospital ethics committees has been suggested by philosophers, attorneys and the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research.[6-8] Some authors, however, have wondered if the principles of clinical ethics can be used to help make clinical decisions in patient care.[10]

To address the need for ethical analysis and advice, a board-certified internist in a clinical ethics fellowship provided formal clinical ethics consultations in a university teaching hospital. To learn more about the types of cases that required analysis and assistance, we reviewed 27 consecutive, unsolicited clinical questions we received about individual patients, together with the ethical issues identified.*

### Methods

All 27 consultations done from July 1985 to June 1986 during a fellowship in clinical ethics were retrospectively reviewed and analyzed. Although a formal consultation service did not exist, staff and house-staff physicians requested ethical assistance from clinicians in the Center for Clinical Medical Ethics (University of Chicago). When a consultation was requested, information was gathered by the clinical ethics fellow based on a model outline for ethics consultation (Figure 1). First, historical and laboratory information was gathered from the chart. The referring physicians were interviewed. The patient was then examined and, if able to communicate, was interviewed. Health care workers, family members, administrators and "significant others" were interviewed as needed. After the data had been gathered, the primary ethical issues were assessed. After discussing the issues with an attending physician-ethicist, suggestions were made for resolving the clinical question. References to legal precedents, hospital policies and the relevant medical and clinical ethics literature were cited and made available to the requesting service. The consultant either arranged or conducted (or both) family meetings, team meetings and case conferences in nearly all cases. Written consultations were placed in the progress notes and entitled "Clinical Ethics" or "Consultation Clinical Ethics."

The clinical question and primary ethical issue were identified in each consultation. The clinical question, posed by the referring physicians—such as, "Can we write a do-not-resuscitate order?"—was recorded at the beginning of each consultation report. The primary ethical issue identified by the consultant in his or her assessment or discussion—such as ethically appropriate indications for the order to not resuscitate—was defined using a basic method of clinical ethical decision making.[9]

*A Case Example of an Ethics Consultation*

*Case 3.* The patient, a 65-year-old woman with metastatic breast carcinoma, had been treated with chemotherapy, radiotherapy and surgical therapy. During her sixth week in hospital, she was transferred from another service to the medical intensive care unit (ICU) for treatment of sepsis. In her seventh hospital week, the patient refused the removal of a chest tube, placed for an empyema, saying that she wanted "no more surgery."

An ethics consultation was obtained to assess the patient's competency to refuse treatment. The consultant reviewed the chart, spoke with and examined the patient and interviewed physicians, ICU nurses and members of the family. The consultant noted that a prolonged hospital stay and the use of cimetidine, narcotic and benzodiazepine may alter a person's mental state. On examination with her son in the room, the patient knew and spoke of her previous pneumothorax, its new resolution and her continued immobilization by the chest tube if it remained. She did not know the procedure for chest tube removal.

The consultant found the patient to be competent but uninformed. The consultant also addressed her physicians' discomfort with the clinical situation. The consultant discussed with the team its frustration with the patient's severe physical illness, their discomfort with the "politics" of the patient transfer and their revulsion by her postoperative chest wall deformity.

The patient's competence was later affirmed by the medical team. One physician then explained the procedure for chest tube removal to the patient and her son together. The patient was reassured by her son that "surgery" was not

*Steven H. Miles, MD, provided invaluable assistance with analysis.

(La Puma J: Consultations in clinical ethics—Issues and questions in 27 cases. West J Med 1987 May; 146:633-637)

From the Center for Clinical Medical Ethics, the Division of the Biological Sciences, University of Chicago, and the Department of Medicine, The Pritzker School of Medicine, Chicago.

Dr La Puma is a Senior Fellow in Clinical Ethics and General Internal Medicine. This work was supported in part by the Henry J. Kaiser Family Foundation.

Reprint requests to John La Puma, MD, Senior Fellow, Center for Clinical Medical Ethics, Department of Medicine, Box 72, University of Chicago Hospitals, 5841 S Maryland Ave, Chicago, IL 60637.

involved. She then consented to the chest tube removal, before which the cimetidine and diazepam therapy was discontinued. The patient eventually recovered to leave the hospital.

## Results

In all, 24 staff and house-staff physicians referred 27 patients for consultation (Table 1). Of the 27 patient referrals, 16 (59%) came from physicians in the Department of Medicine and 11 (41%) came from physicians in surgery, neurology, pediatrics and obstetrics/gynecology. Attending physicians made 16 referrals and house officers 11.

Patients ranged in age from 8 to 95 years (median 48.1); 12 (44%) were in the ICU, and 13 (48%) were able to communicate, verbally or nonverbally, with the consultant at the initial visit.

Of the 27 questions referred, 18 (67%) concerned the withholding or withdrawing of life-sustaining therapies; 7 of these specifically concerned orders not to resuscitate. Questions about the appropriateness of mechanical ventilation, intensive care, hemodialysis, feeding and hydration, antibiotics, heart and liver transplantation were among those received. Three questions of disagreement (physician-physician, physician-family and patient-family) were also received (Table 2).

Consultation requests always reflected a clinical question, although the consultant did not always identify it as the primary ethical issue. For example, in case 8, a competent 38-year-old man had previously refused therapy for metastatic penile carcinoma now infiltrating his left femoral artery. In the emergency department, his systolic blood pressure was 80 mm of mercury and his hemoglobin was 4 grams per dl. After transfusion and admission to the hospital, an ethics consultation was requested. The clinical question concerned the financial cost of additional units of blood and their perceived futility. In this case, the medical team's disappointment with this previously treatable, now terminal patient influenced the team's ability to separate individual patient need from the cost of needed medical care. Because of the patient's irreversible disease, the consultant advised that the most important concern was appropriate terminal care and that the patient's wishes about life-sustaining treatment should be sought. Once informed about his disease, the patient refused cardiopulmonary resuscitation. A do-not-resuscitate order was written and the patient died on the fourth hospital day.

In many cases, the consultant was able to help the referring physician identify other ethical issues not previously recognized. In case 17, for example, a resident and an attending physician disagreed about the appropriateness of a do-not-resuscitate order for a 68-year-old lethargic woman three weeks after she had suffered a middle cerebral artery embolism and massive stroke. She had worked in a nursing

- Question(s) asked, quoted
- Name and position of referring physician
- Summary of present illness and hospital course, with relevant consultant reports, patient disabilities and prognosis
- Present medications
- Family and personal history
  - Functional status and primary relationships, including "significant others" and caretakers if appropriate, before hospital admission
  - Family members' involvement in patient's care
  - Family interests, objectives and needs regarding patient and patient's illness and potential conflicts with patient's interests, objectives and needs
  - Patient's expressed preferences, with interests, objectives and needs regarding life processes, including present illness
  - Verifiable advance directives or proxy decision makers
  - Patient's religious views, if "religiously active"
- Physical examination, with special attention to
  - Mental state and competency to participate in health care decision making
  - Critical organ function—heart, lungs, kidneys and liver
  - Neurologic function
- Laboratory review, with special attention to
  - Reversible causes of depressed neurologic function or abnormal mental state
  - Critical organ function—heart, lungs, kidneys and liver
- Assessment of ethical issues, with discussion
  - Medical indications
  - Patient preferences
  - Socioeconomic considerations
  - Quality of life considerations
- Suggested answers to the clinical question(s) and approaches to the ethical issues identified
- Signature
- References

**Figure 1.**—Ethics consultation format.*

*Mark Stegler, MD, provided assistance in designing the format for the figure.

TABLE 1.—*Patients Referred for Ethics Consultation*

| *Patients, in Order of Consultation* | *Age, Years* | *Sex* | *Primary Diagnosis* |
|---|---|---|---|
| 1 . . . . | 72 | ♂ | Probable lung cancer |
| 2 . . . . | 60 | ♂ | Squamous cell carcinoma, unknown primary |
| 3 . . . . | 65 | ♀ | Adenocarcinoma, breast |
| 4 . . . . | 25 | ♂ | Cirrhosis with encephalopathy |
| 5 . . . . | 38 | ♂ | Gram-negative endocarditis |
| 6 . . . . | 55 | ♀ | Squamous cell carcinoma, breast |
| 7 . . . . | 73 | ♂ | Meningioma, after resection |
| 8 . . . . | 38 | ♂ | Squamous cell carcinoma, penis |
| 9 . . . . | 8 | ♂ | Chronic postmeningitic state |
| 10 . . . . | 58 | ♂ | Acute nonlymphocytic leukemia |
| 11 . . . . | 33 | ♂ | Subarachnoid hemorrhage |
| 12 . . . . | 33 | ♀ | Thalamic hemorrhage |
| 13 . . . . | 63 | ♀ | End-stage renal disease, idiopathic |
| 14 . . . . | 68 | ♀ | Uterine sarcoma |
| 15 . . . . | 60 | ♀ | Anoxic encephalopathy |
| 16 . . . . | 20 | ♀ | Coma, after viral encephalitis |
| 17 . . . . | 68 | ♀ | Severe cerebrovascular accident |
| 18 . . . . | 44 | ♀ | Acute subarachnoid hemorrhage |
| 19 . . . . | 58 | ♀ | Progressive systemic sclerosis |
| 20 . . . . | 27 | ♀ | Spinal cord astrocytoma |
| 21 . . . . | 55 | ♂ | Hepatocellular carcinoma |
| 22 . . . . | 26 | ♂ | Idiopathic cardiomyopathy |
| 23 . . . . | 10 | ♂ | Anoxic encephalopathy |
| 24 . . . . | 38 | ♂ | Prosthetic valve endocarditis |
| 25 . . . . | 83 | ♀ | Anoxic encephalopathy |
| 26 . . . . | 25 | ♀ | Staphylococcal endocarditis; positive for human immunodeficiency virus |
| 27 . . . . | 95 | ♀ | Urosepsis |

home and cared for many chronically ill patients. She had lived with her daughter and a sister with whom she had spoken only generally about various patients at work. Incompletely recognized ethical issues here included the appropriate role of the family in the care of an incompetent patient and the nature of advance directives for life-sustaining therapy. In this case, the consultant advised that the patient's prognosis for recovery be clearly documented before limiting any treatment. The physicians' goals of treatment should have been oriented towards alleviating symptoms, rather than curing disease, if there was no improvement within a reasonable and defined time period.

*Reasons for Consultation*

*Assistance in decision making.* Assistance in decision making was one of several reasons for consultation. In case 1, for example, a 72-year-old lethargic man with a large right apical mass and atelectasis of the right upper lobe was admitted to the ICU. Bronchoscopy showed an obstructing lesion of a segmental bronchus; cytology showed no acid-fast bacilli but findings were strongly suggestive of malignancy. In this case, the consultation was requested to analyze and affirm the physicians' judgment that a do-not-resuscitate order was appropriate for a patient who appeared to be terminally ill, but whose cytology results were nondiagnostic. The consultant suggested that futility of treatment was an ethically appropriate indication for a do-not-resuscitate order and, given the medical data, such an order was appropriate. The order was written, and the patient died three days later.

*Assistance in case management.* A second reason for consultation was assistance in case management. In case 13, a 63-year-old woman suffered idiopathic renal failure and severe neuropathy. Sural nerve and renal biopsies showed only "degeneration"; hemodialysis and every-two-hour turning were required. The patient, still competent five months after admission and diagnosis, requested hospital discharge despite inadequate home nursing care. Here physicians sought an independent analysis of the patient's competency and morally justifiable potential solutions to the question of hospital discharge. Several alternative solutions were provided (additional home health care, hospice support), and, after a week, the patient left the hospital in the care of her son.

*Assistance in resolving disagreements.* A third reason for consultation was to help resolve disagreements between patient and family, physicians and family and between two physicians. In case 14, for example, the physician and the patient's daughters disagreed about dialysis for a 68-year-old semicomatose woman with uterine sarcoma refractory to therapy. The consultant noted that the physician's overall treatment goals had changed from an attempted cure to comfort as it became clear that the patient was dying. The daughters had not previously been informed of their mother's terminal condition and insisted on dialysis. The consultant helped to resolve the physician-family disagreement by mediating a discussion between the daughters and the physician. The patient's prognosis and the changing goals of therapy were clarified for the family by the physician. The physician did not order hemodialysis, the family agreed and the patient died within 24 hours of the discussion.

## Discussion

The referred cases involved a broad range of issues, most of which focused on questions of foregoing one or more life-sustaining therapies in seriously ill patients. The clinical eth-

TABLE 2.—*Questions Asked, Issues Perceived and Their Correlation*

| *Patients* | *Clinical Question Asked* | *Primary Ethical Issue Perceived* |
|---|---|---|
| 1 | DNR order appropriate? | Indications for orders not to resuscitate |
| 2 | DNR order appropriate? | Indications for orders not to resuscitate |
| 3 | Patient competent to refuse chest tube removal? | Competency to refuse treatment |
| 4 | DNR order appropriate? | Indications for orders not to resuscitate |
| 5 | DNR order appropriate? | Role of cost in patient care |
| 6 | Withdrawal of treatment appropriate? | Withdrawal of life-sustaining therapy |
| 7 | Withdrawal of intensive care appropriate? | Allocation of scarce resources |
| 8 | Cost concerns appropriate? | Patient's refusal of treatment |
| 9 | DNR order appropriate? | Indications for orders not to resuscitate |
| 10 | DNR order appropriate? | Autonomy of a competent patient |
| 11 | Withholding feeding tube appropriate? | Indications for withholding life-sustaining therapy |
| 12 | Withholding feeding tube appropriate? | Indications for withholding life-sustaining therapy |
| 13 | Patient *v* family re: placement | Autonomy of a competent patient |
| 14 | Physician *v* family re: dialysis | Indications for withholding life-sustaining therapy |
| 15 | Withholding nutrition, resuscitation, mechanical ventilation appropriate? | Brain death *v* chronic vegetative state |
| 16 | Further aggressive treatment appropriate? | Roles of an acute-care institution |
| 17 | Attending MD *v* resident MD re: DNR order | Indications for orders not to resuscitate |
| 18 | Withdrawal of vasopressors, ventilator appropriate? | Indications for withholding life-sustaining therapy |
| 19 | Withholding of nutrition, withdrawing of hydration appropriate? | Recognition of a terminally ill state |
| 20 | Mechanical ventilation appropriate? | Autonomy of a competent patient |
| 21 | HMO obligated to pay for liver transplant? | Indications for experimental therapy |
| 22 | Psychosocial criteria valid for heart transplantation? | Allocation of scarce clinical resources |
| 23 | Withdrawal of ventilator appropriate? | Indications for withdrawing life-sustaining therapy |
| 24 | Responsibility for long-term care? | Principles of palliative medical care |
| 25 | Withdrawal of ventilator, TPN antibiotics appropriate? | Indications for withholding life-sustaining therapy |
| 26 | Responsibility to warn public contacts? | Confidentiality: when to breach |
| 27 | DNR order appropriate? | Indications for orders not to resuscitate |

DNR=do not resuscitate, HMO=health maintenance organization, MD=physician, TPN=total parenteral nutrition

ical issues in these cases form the beginning of a basic curriculum in medical ethics; most have been identified as essential topics for medical school curricula.[11]

Three major reasons for consultation requests were identified. The first, assistance in decision making, was in some cases simple reassurance that a physician's own decision was morally justifiable; in other cases, physicians were genuinely puzzled by complex patient cases. In these latter cases, assistance in case management was requested. Here the consultant played an especially active role, suggesting the appropriateness of ventilator withdrawal or the institution of proper pain medication. Third and finally, assistance in resolving disagreements required the consultant to be a type of diplomatic liaison and help the disagreeing parties reach mutually acceptable conclusions.

Our consultations were practical, clinical and educational. During the consultative process, physicians were helped to think through difficult ethical issues and improve their decision-making skills. In each case, the consultant attempted to integrate the consultative process with the case synthesis. More instructive than the written report or citations from the medical literature were the interactions between the consultant and the health care team. It is one thing to didactically teach ethically appropriate indications for do-not-resuscitate orders or withdrawing life support. It is quite another to work alongside physicians on the wards and consider a particular patient at the bedside.

Experience as a clinician was invaluable in doing consultations. The ethics consultant's knowledge of patient care has been noted to promote his or her acceptance by referring physicians.[12] Clinicians, including some nonphysicians, understand nuances and dynamics of patient care and arrive at that understanding by bedside observation and experience.[13] Recognizing the uniqueness of an individual patient's problems and knowing that medical care is based on medical need are at the heart of being a consultant-ethicist.

It may seem to some that any wise and experienced clinician could do ethics consultations. Clinicians who are both wise and experienced know well the need to balance the technical and the moral aspects of patient care. Regardless of how wise an individual physician may be, however, most physicians in teaching hospitals have had relatively little experience in analyzing moral problems. Teaching practicing physicians to build their own conceptual framework for decision making is the duty of many consultants in medicine. A physician-ethicist can teach the relevant fundamental concepts and special language of ethics, while helping physicians develop a structured and coherent strategy for the analysis of ethical problems that arise daily in clinical practice.

Further, an ethics consultant has the specific task of bringing together disparate or incompletely known parts of a given patient's medical course and social history. With medicine's developing technologic capabilities, hospitals primarily provide technical services. Busy physicians, even those with an interest in ethics, may tend to marginalize patients' personal values and histories, with these data falling to the side, especially when a patient is critically ill. The ethics consultant has the special training and professional charge to help gather the relevant data and restore a central ethical focus to a given case.

Physicians obtained consultations by contacting in person the clinical ethics fellow or an attending physician. A Pediatrics Bioethics Committee, developed in response to federal "Baby Doe" regulations, exists at our institution, but there is no adult ethics committee. The pediatric consultations were not discussed with the Bioethics Committee. Hindered by variable standards of membership and uncertain legal liability, ethics committees generally have not been able to successfully assume active consultative roles.[14,15] Our consultation team was able to respond promptly to physician referrals and brought to the bedside both medical understanding and ethical insight. Few ethics committees have either the time or inclination to analyze a patient's chart or examine a patient and suggest recommendations for care. With their multidisciplinary membership and administrative orientation, many ethics committees are well equipped to consider problematic hospital policies and less well equipped to consult in individual patient cases.[16]

Ethicists in medicine are not new, although consultant physician-ethicists doing written consultations are. A National Institutes of Health-University of California, San Francisco, conference on ethics consultation was convened in October 1985.[17] It was attended by 53 ethicists, each having been identified by his or her institution as a consultant. The invited consultants were surveyed: 20 held PhDs, 6 MDs, 5 MAs, 4 JDs, 3 RNs and 6 held other degrees. Of 38 respondents, 20 kept records of their consultations. Only 15 wrote in patient charts; only 8 reported making medical rounds.

Physicians may express reservations about ethics consultation. They may fear possible legal liability in not following a consultant's written advice[15] or the loss of case-management autonomy. Many may doubt the actual usefulness of ethical analysis and advice. In this series of 27 cases, we received many positive comments for our clinical assistance and educational approach. Little data exist on the efficacy of ethics consultations or general medical consultation,[18] although Perkins and Saazthoff showed that ethics consultations "sometimes change patient management and almost always boost physician confidence in the final treatment plan."[4] Clearly, more research is needed to determine the usefulness of consultations, perhaps using follow-up evaluations from both consultant and referring physicians.

There are many important unanswered questions about ethics consultations: Who should do them? How should they be done? What skills should a consultant have? Perhaps the most important question is the most basic: What is the goal of an ethics consultation? Should ethics consultants become involved in issues of institutional policy making,[19] or do clinical work and teach clinical ethics to physicians at the bedside?[20]

Consultants in clinical ethics should be competent in both medicine and ethics and have strong interpersonal and communications abilities. Clinical ethicists should teach decision-making skills to practicing physicians during each consultation. Decision-making skills in clinical ethics are practical skills, as medicine is primarily patient care, distinguished from the humanities and the sciences by its practical purpose.[21] Clinical ethicists in a hospital can help physicians reach ethical solutions in a broad range of difficult cases.

#### REFERENCES

1. Jonsen AR: Can an ethicist be a consultant? *In* Abernathy V (Ed): Frontiers in Medical Ethics: Applications in a Medical Setting. Cambridge, Mass, Ballinger, 1980, pp 157-171

2. Rothenberg LS: Clinical ethicists and hospital ethics consultants: The nature and desirability of their clinical role. *In* Fletcher J, Jonsen AR (Eds): Proceedings of the Conference on Ethics Consultation at the National Institutes of Health. Ann Arbor, Mich, Health Administration Press, 1987, in press

3. Purtilo RB: Ethics consultations in the hospital. N Engl J Med 1984; 311:983-986

4. Perkins HS, Saazthoff BS: How do ethics consultations benefit clinicians? (Abstr). Clin Res 1986; 34:831A

5. Winkenwerder W Jr: Ethical dilemmas for housestaff physicians—The care of critically ill and dying patients. JAMA 1985; 254:3454-3457

6. President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research: Deciding to Forego Life-Sustaining Treatment: Ethical, Medical and Legal Issues in Treatment Decisions. Government Printing Office, 1983

7. Cranford RE, Doudera AE: The emergence of institutional ethics committees, chap 1, Institutional Ethics Committees and Health Care Decision-Making. Ann Arbor, Mich, Health Administration Press, 1984, pp 5-21

8. Thomasma DC: Ethics committees in hospitals; Alternative structures and responsibilities. QRB 1984; 10:6-10

9. Jonsen AR, Siegler M, Winslade WJ: Clinical Ethics, 2nd Ed. New York, MacMillan, 1985

10. Glover JJ, Ozar DT, Thomasma DC: Teaching ethics on rounds: The ethicist as teacher, consultant and decision-maker. Theor Med 1986; 7:13-32

11. Culver CM, Clouser KD, Gert B, et al: Basic curricular goals in medical ethics. N Engl J Med 1985; 312:253-256

12. Volpintesta EJ, Schechter JP: Ethics consultants nced doctors' support. Hastings Cent Rep 1986; 16:48

13. Tumulty PA: What is a clinician and what does he do? N Engl J Med 1970; 283:20-24

14. Siegler M: Ethics committees: Decisions by bureaucracy. Hastings Cent Rep 1986; 16:22-24

15. Wolf SM: Ethics committees in the courts. Hastings Cent Rep 1986; 16:12-15

16. Annas GJ: Refusal of lifesaving treatment for minors. J Fam Law 1984-1985; 23:218-240

17. Bermel J: Ethics consultants: A self-portrait of decision makers. Hastings Cent Rep 1985; 15:2

18. Ballard WP, Gold JP, Charlson ME: Compliance with the recommendations of medical consultants. J Gen Intern Med 1986; 1:220-224

19. Cassel CK: Doctors and allocation decisions: A new role in the new medicare. J Health Polit Policy Law 1985; 10:549-564

20. Siegler M: A legacy of Osler: Teaching clinical ethics at the bedside. JAMA 1978; 239:951-956

21. Pellegrino ED: Towards a definition: A philosophy of medicine. J Med Philos 1986; 11:9-16

# Informed Opinion

## Physicians and the Death Penalty

KIM MARIE THORBURN, MD, *Honolulu*

Do physicians participate in the death penalty in the United States? Is there ever ethical justification for physician involvement? The growing number of executions creates ethical challenges for prison physicians as well as those in other fields of medicine. The ethical questions that the death penalty poses for physicians contrast responsibility to the individual against duty to society. In this article I examine examples of the medical profession's connection with the death penalty in the United States and analyze the ethical permissibility of the involvement.

Beneficence, a guiding principle of medical ethics, calls for assisting others in need and avoiding harm.[1] Physicians' foremost duty is to their patients. There are situations in which the duty to serve society outweighs certain responsibilities to individual patients, and often such situations are codified in laws. For example, laws that require reporting cases of contagious diseases violate patient privacy, but the decisive duty is to protect the public from the spread of disease. Conflicts may arise when laws or regulations require actions by physicians that are contrary to the duty of beneficence and that cannot be justified by evoking a greater duty to society.

### The Execution

The legislation of lethal-injection executions seeks a humane method of killing. It could be argued that physicians involved in lethal-injection executions serve an ethical duty by providing a painless method of death for legally condemned persons. Many medical organizations, including the American Medical Association, the World Medical Association and numerous state medical associations, recognizing fallacy in the argument that physicians serve an ethical duty by humane killing with lethal doses of drugs, have passed resolutions prohibiting physician participation in executions, except to certify deaths.[2,3] Although physician participation in executions is not defined by the resolutions, it is evident that injecting lethal doses of drugs is not permitted. Some physicians have, however, examined the victims to select sites for venipuncture and have assisted in obtaining the drugs.[4,5]

Most states require physician attendance at executions. One role of the physician in attendance is to certify death. A stethoscope is strapped over the chest of the condemned person and the physician pronounces the time of death when the heart stops beating.

Attendance at an execution to certify death can lead to direct participation by a physician. Amnesty International, which opposes the death penalty, recently questioned the physician's involvement in the Indiana electrocution of William Vandiver (Amnesty International USA, "Medical Action," 1985 Oct 29). The physician reportedly heard Vandiver's heart still beating after the first jolts of electricity. When the physician diagnosed persistent vital signs, more shocks were delivered. It can be argued that by using his medical skills, the physician actually directed the killing of the victim.

### Death Row

Difficult ethical decisions for physicians may occur during the treatment of death row inmates. In December 1983, condemned inmate Manuel Quintana died of ischemic heart disease at the Medical College of Virginia Hospital (Richmond, Va).[6] In March 1983, a coronary artery bypass operation had been recommended to Quintana by a cardiovascular surgeon who believed the ill man would have a very good outcome. Quintana was originally scheduled to be electrocuted in August 1983, but prison officials were willing to pay for the operation. Quintana refused the operation. His refusal of treatment was probably the result of a potentially reversible depression. His treating physicians were forced to decide whether intervention was appropriate to sustain a condemned life, especially when state-imposed death seemed so imminent.

Condemned inmates are at risk for suicide. In most cases, prevention of suicide clearly serves the duty of beneficence. When an inmate on California's death row hoarded his prescribed antidepressant medication and took a lethal overdose, prison medical officials responded by changing the method of medication distribution to ensure against hoarding. The California case shows the challenge of preventing suicide by condemned persons. Is the intervention merely to serve the state, or is it aimed at benefiting the person? A death conviction is like a fatal disease. As in other terminal conditions, the physician's goal in treatment may more appropriately be relief of suffering than aggressive prevention of suicide.

### Ford Versus Wainwright

In June 1986, the United States Supreme Court gave its long-awaited ruling in Ford *v* Wainwright. One of the questions of the case was the constitutionality of executing insane persons. Before the Ford ruling, most states had laws proscribing execution of insane persons, but there was no legal precedent that such a practice violated the Eighth Amendment prohibition of cruel and unusual punishment.

Alvin Ford has been on Florida's death row since 1974 when he was convicted of killing a Fort Lauderdale policeman. Apparently Ford was sane when convicted and sen-

(Thorburn KM: Physicians and the death penalty. West J Med 1987 May; 146:638-640)

From the Department of Medicine, University of Hawaii John A. Burns School of Medicine, Honolulu.

Dr Thorburn was a physician for several jails and prisons in California before assuming her current position as Associate Professor of Medicine at the University of Hawaii where she directs the health services of the Oahu Community Correctional Center and provides consultation for the state's Division of Corrections. The opinions expressed herein are those of the author and are not to be construed as the official views of the University of Hawaii or the Hawaii Division of Corrections.

Reprint requests to Kim Marie Thorburn, MD, Department of Medicine, John A. Burns School of Medicine, University of Hawaii at Manoa, 1960 East-West Road, Honolulu, HI 96822.

tenced, but now he believes that he is Pope John III and owner of the prison. In accordance with Florida's procedure before the Supreme Court ruling, the governor, after consulting with three state-appointed psychiatrists, declared Ford sane and ordered his execution. A psychiatrist hired by Ford's lawyer found the condemned man delusional, psychotic and incapable of understanding his crime or the punishment. The results of the examination by the defense were not considered by the governor in his certification of sanity (Hager P, "Execution of Insane Prisoners Banned by Supreme Court," *Los Angeles Times,* 1986 June 27, p 18).

The significance of the Ford case for physicians is the five to four decision that executing insane persons represents cruel and unusual punishment and is therefore prohibited under the Constitution. The Ford ruling presents a dilemma for psychiatrists who may now be required to examine all condemned persons before execution. A psychiatrist who finds no mental illness or who recognizes capacity to understand the crime and punishment sends the patient to death. After a psychiatrist diagnoses mental illness during a competency-to-be-executed evaluation, a course of treatment could remit the mental illness enough to make the patient's execution possible. Thus, the treating physician, whose duty is to relieve suffering, becomes responsible for administering a course that ends in the death of the patient.

The dissenting opinion in the Ford case expressed concern that there will now be widespread faking of mental illness among death row inmates. What is a psychiatrist's role in diagnosing malingering among condemned inmates? Does malingering among inmates on death row present a situation in which the psychiatrist's greater duty is to serve the state rather than the patient?

The psychiatrist's responsibility in detecting malingering was an issue in Aaron Mitchell's execution in April 1967, the last in California. The day before his death, Mitchell cut his wrists and wrote "I am Christ" in his blood on the walls of his cell. He had to be carried, kicking and screaming that he was Christ, to the gas chamber. The psychiatrist informed prison authorities that his evaluation indicated that Mitchell was feigning delusions to avoid being executed (Kroll M., "The Room With No Exit," *California Living Magazine,* 1984 Mar 4, pp 25-27, 30, and Orwin M., " Last Man Executed in California—Furor Over Mitchell Case Resounds 18 Years Later," *Los Angeles Times,* 1985 Aug 23, pp 1, 22).

## Aggravating Circumstances

In 1972, in Furman *v* Georgia, the United States Supreme Court, in a five to four decision, declared all the extant death penalty laws unconstitutional in application. The majority wrote five separate opinions in the Furman case. Justices Marshall and Brennan concluded that the death penalty per se violated the Eighth Amendment. The other three justices of the majority (Stewart, Douglas and White) focused their opinions on the disproportionality of applying the death penalty. The laws, according to the Furman ruling, represented cruel and unusual punishment because death sentences were "so wantonly and so freakishly imposed" and "only a small and capricious selection of offenders have been put to death."[7]

Almost immediately after the Furman ruling, states sought to reinstitute death penalty laws that could be predictably and reasonably applied. The penalty phase of the trial is now separated from the judgment, and a wide range of evidence is admitted during the penalty phase. In most states, juries are instructed to balance mitigating and aggravating factors about the accused and the crime in determining a sentence of death. During the penalty phase of a capital trial, physicians, including forensic specialists, may give testimony that is instrumental in sentencing the condemned.

TABLE 1.—*Examples of Aggravating Circumstances That Might Call for Medical Testimony*

| |
|---|
| Intent |
| Premeditation |
| Future dangerousness |
| Torture before commission of murder |
| Sexual assault during commission of murder |
| Coincident disease contributing to death during commission of a felony |
| Lying in wait |
| Execution-style murder |

Aggravating and mitigating circumstances are defined in statute and in case law. There are several aggravating circumstances that can be corroborated by medical testimony (Table 1). Medical testimony that supports aggravating circumstances puts a forensic expert in the position of advocating a death sentence.

Speculative expert opinions reflect prejudices, a consideration in the legal controversy that there is proportional application of the death penalty. An example is Leon Brown who went to North Carolina's death row when he was 16 years old. A key consideration in his death sentence was testimony by the medical examiner that the victim's asphyxial death took five minutes (Columbia Broadcasting System, "60 Minutes," 1985 Dec 22). The medical examiner's opinion is controversial. Certainly, loss of consciousness from strangulation occurs rapidly; yet, the implication of torture due to the agonizing duration of suffering influenced the jury's sentence of death.

## The Ethical Decision

Physicians participate in all phases of the death penalty, from trial to execution. Testimony, care of condemned persons, competency examinations and physician witnessing of executions require medical decisions. Medical involvement in executions occurs to relieve society's uncertainty that the ultimate and irreversible punishment can be fairly and justly administered, but this service to society cannot be shown to outweigh the duty of beneficence. The decisive benefit to society of an execution cannot be demonstrated. The principle of beneficence dictates that physicians must not be involved in executions.

The morality of the death penalty can itself be questioned. By international standards, the death penalty is a violation of human rights—extinction of the right to life acclaimed in the Universal Declaration of Human Rights—and the United Nations calls for diminishing the use of the death penalty, leading to abolition.[8] In the United States the opposite is occurring. There were no executions in this country for ten years until 1977. From 1977 through 1982, there were six executions.[9] There were 18 executions in 1985 (Amnesty International USA, "Urgent Action," 1985 Dec 19).

There is overwhelming public support for the death penalty in the United States, with polls showing more than 70% in favor (Balzar J., "The Times Poll: 75% Support Death Penalty in California," *Los Angeles Times,* 1985 Aug 19, pp

1, 12).[9] Yet, the actual act of executing still leads to discomfort among many observers. Throughout history, societies have sought to ease the distress of legal murder by applying more and more "humane" methods of executing.[10] Lethal injection is the latest solution to public discomfiture with executions.[11]

Medical professional associations reflect society's ambiguity about the death penalty. Resolutions against physician involvement in executions have not clearly identified and prohibited participation. It is time for United States medical associations to take a clear stand. *Primum non nocere.* Physician participation in any phase of the death penalty, from trial to execution, is not permissible by medical ethical standards. Even physician attendance at executions to certify death makes the physician a participant. Our medical associations must follow the lead of our Scandinavian colleagues, who state

. . . the medical associations of the Nordic countries (Denmark, Finland, Iceland, Norway and Sweden) in recognition of human integrity declare it indefensible for any physician to participate in any act connected to and necessary for the administration of capital punishment.[12]

#### REFERENCES

1. Jonsen AR, Siegler M, Winslade WJ: Clinical Ethics. New York, Macmillan Publishing, 1982, p 11

2. AMA Judicial Council: Report to the House of Delegates—129th Annual Convention. Chicago, American Medical Assoc, 1980

3. Lisbon Resolution on Physician Participation in Capital Punishment—34th Assembly. Ferney-Voltaire, France, World Medical Assoc, 1981

4. Carrell S: Execution controversy faces physician. AMA News 1983 Jan 21, pp 25-26

5. Lefton D: Execution of Texas prisoner raises ethical issues for MDs. AMA News 1982 Dec 17, pp 1, 16

6. Hoffer W: Medical care on death row—Awaiting execution, Manuel Quintana refused bypass surgery. AMA News 1984 Mar 9, pp 21-22

7. *Furman v Georgia,* 408 US 238 (1972) (Stewart J concurring)

8. United Nations General Assembly: Resolution 32/61 1977

9. Bruck DI: The Death Penalty in the United States. New York, Amnesty International USA, 1987

10. Camus A: Reflections on the guillotine, Resistance, Rebellion, and Death. New York, Vintage Books, 1974, pp 173-234

11. Bayer R: Lethal injections and capital punishment: Medicine in the service of the state. J Prison Jail Health 1984; 4:7-15

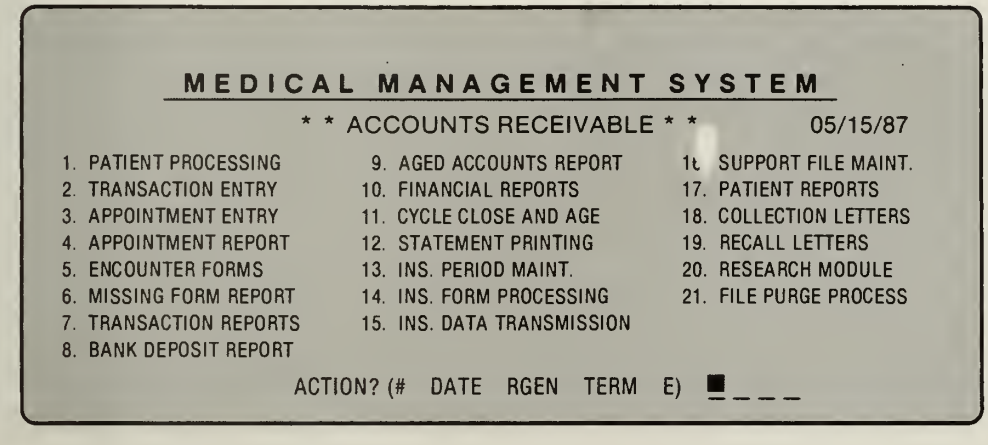
12. Hovedbestyrelsen: Nordisk resolution om laegers medvirken ved henrettelser. Ugeskr Laeger 1986; 148:1929

# ALL COMPUTER COMPANIES KNOW COMPUTERS

## BUT HOW MANY OF THEM KNOW THE MEDICAL OFFICE?

It's one thing to know computers inside and out,
and quite another to know how to
adapt that computer to the needs of your practice.

## AT SIERRA MEDICAL SYSTEMS WE UNDERSTAND THE MEDICAL OFFICE.




**SOFTWARE:** Proven since 1976 complete with Patient Accounts Receivable, Patient Statements, Insurance Billing, Appointment Processing, Electronic Claims Processing, Medical Research, Financial Reporting, Collection Letters, Recall, Report Generator, Links to Word Processing and Financial Modeling, General Accounting, and much more are all part of this state of the art system.

**HARDWARE:** The IBM* AT or compatible NCR*, BASIC FOUR*, FORTUNE*, and others provide true multi-user, multi-tasking computer systems.

**SUPPORT:** SIERRA MEDICAL SYSTEMS currently supports over 800 physicians in California by providing total system care for both software and hardware. Sierra Medical Systems provides full training for the medical office, plus a complete customer service staff to help you after your training is completed. Technical support is also provided via modem.

**RESPOND:** For more information or a personal demonstration of the Sierra Medical System call today.

* **IBM** - is a trademark of IBM Corporation
* **NCR** - is a trademark of NCR Corporation
* **BASIC FOUR** - is a trademark of MAI Basic Four, Inc.
* **FORTUNE** - is a trademark of Fortune Systems Corporation

**SIERRA MEDICAL SYSTEMS**
A DIVISION OF ATEK

**Headquarters:**
3017 Kilgore Road, Suite 180
Rancho Cordova, CA 95670
(916) 638-4744 • (415) 785-5777

CONTINUING MEDICAL EDUCATION

(Continued from Page 563)

## RADIOLOGY

June 10-13—**Advanced Echocardiography and Doppler Ultrasound—1987.** American College of Cardiology at Sheraton Harbor Island East, San Diego. Wed-Sat. Contact: Mary Anne McInerny, ACC, 9111 Old Georgetown Rd, Bethesda, MD 20814. (301) 897-5400, ext 226.

June 14-16—**1987 Radiology US Open Golf Meeting.** UCSF at Hyatt Regency, San Francisco. Sun-Tues. Contact: UCSF.

August 3-7—**Diagnostic Radiology Seminars.** UCSF at Hyatt Regency, Maui, Hawaii. Mon-Fri. 27.5 hrs. $495. Contact: UCSF.

August 13-15—**Advanced Ultrasound.** American College of Obstetricians and Gynecologists at Silverado Inn, Napa. Thurs-Sat. Contact: Robin Murray, ACOG, 600 Maryland Ave SW, Washington, DC 20024-2588. (202) 638-5577.

August 22-29—**Radiology.** USC at Maui Marriott Hotel, Maui, Hawaii. One week. 26 hrs. $525. Contact: USC.

August 26-28—**Interventional Radiology.** UCSF at Hyatt Regency Hotel, San Francisco. Wed-Fri. Contact: UCSF.

August 29-30—**Advances in Imaging Technology.** UCSF at Hyatt Regency, San Francisco. Sat-Sun. Contact: UCSF.

September 10-12—**Contemporary Diagnostic Imaging: CT, Interventional, MRI, US.** UCSF at Hyatt Regency, Monterey. Thurs-Sat. Contact: UCSF.

September 17-19—**Ultrasound Workshop.** UCSF at San Francisco. Thurs-Sat. Contact: UCSF.

October 17-18—**Magnetic Resonance Imaging for Technologists.** UCSF at Hyatt Regency Hotel, San Francisco. Sat-Sun. Contact: UCSF.

October 19-23—**Clinical Magnetic Resonance Imaging.** UCSF at Hyatt Regency Hotel, San Francisco. Mon-Fri. $495. Contact: UCSF.

## SPORTS MEDICINE

May 27-30—**American College of Sports Medicine 34th Annual Meeting.** Bally's Las Vegas Hotel, Nevada. Wed-Sat. Contact: Eileen T. Sexton, PO Box 1440, Indianapolis, IN 46206-1440. (317) 637-9200.

July 27-31—**Sports Medicine Update—1987.** UCSD at San Diego Princess Hotel, Vacation Village. Mon-Fri. 29.5 hrs. $325. Contact: UCSD.

## SURGERY

May 18-21—**Cochlear Implant Training—1987.** House Ear Institute, Los Angeles. Mon-Thurs. 24 hrs. $250. Contact: Antonio De la Cruz, MD, House Ear Institute, 256 S Lake St, Los Angeles 90057. (213) 483-4431.

June 4-5—**16th Annual Neurosurgical Postgraduate Course.** UCSF at San Francisco. Thurs-Sat. 15 hrs. Contact: UCSF.

June 5-6—**6th Annual Southwestern Regional Cutaneous Flap Workshop.** UCLA at UCLA. Fri-Sat. 11 hrs. Contact: UCLA.

June 14-20—**Temporal Bone Surgical Dissection—1987.** House Ear Institute, Los Angeles. Sun-Sat. 62 hrs. $950. Contact: Antonio De la Cruz, MD, House Ear Institute, 256 S Lake St, Los Angeles 90057. (213) 483-4431.

September 14-17—**Cochlear Implant Training—1987.** House Ear Institute, Los Angeles. Mon-Thurs. 24 hrs. $250. Contact: Antonio De la Cruz, MD, House Ear Institute, 256 S Lake St, Los Angeles 90057. (213) 483-4431.

October 4-10—**Temporal Bone Surgical Dissection.** House Ear Institute, Los Angeles. Sun-Sat. $750-950. Contact: Antonio De la Cruz, MD, Director of Education, House Ear Institute, 256 S Lake St, Los Angeles 90057. (213) 483-4431.

October 18-24—**Temporal Bone Surgical Dissection—1987.** House Ear Institute, Los Angeles. Sun-Sat. $750-950. Contact: Antonio De la Cruz, MD, Director of Education, House Ear Institute, 256 S Lake St, Los Angeles 90057. (213) 483-4431.

## OF INTEREST TO ALL PHYSICIANS

May 15-16—**Issues in Identification, Amplification and Rehabilitation With the Hard of Hearing, School-Aged Child.** UCI. Fri-Sat. 10 hrs. Contact: UCI.

May 20-23—**Physical Diagnosis: An Intensive Review.** Memorial Medical Center of Long Beach at Long Beach. Wed-Sat. 28 hrs. Contact: Beverly Ritchie, Memorial Medical Center of Long Beach, 2801 Atlantic Ave, PO Box 1428, Long Beach 90801-1428. (213) 595-2311.

May 26-30—**14th Annual Joint UCLA-Santa Monica Hospital Medical Center Family Practice Refresher Course and Board Examination Review.** UCLA at Miramar-Sheraton Hotel. Tues-Sat. 35.5 hrs. $415. Contact: UCLA.

June 4-6—**Alcohol Problems in the Workplace: Beyond Employee Assistance.** UCSD at Kona Kai Resort Hotel, San Diego. 13.5 hrs. Thurs-Sat. Contact: UCSD.

June 8-13—**UCI Family Practice Refresher Course.** UCI at Newport Beach. Mon-Sat. Contact: UCI.

June 11—**AIDS: Issues for the Primary Care Physician.** Alta Bates Hospital, Berkeley. Thurs. 5 hrs. $40. Contact: Mary Grim, Alta Bates Hospital, 3001 Colby St, Berkeley 94705. (415) 540-1420.

June 14-19—**Fingers to the Toes: Orthopaedics for Primary Care.** UCD at Stanford Sierra Camp, Fallen Leaf Lake. Sun-Fri. 36 hrs. Contact: UCD.

June 15-19—**Sexually Transmitted Disease (STD) Clinician Training Course—Advanced.** Long Beach Health Dept at Long Beach. Mon-Fri. Contact: Anne-Renee Heningberg, Long Beach STD Trng Ctr, PO Box 6157, Long Beach 90806. (213) 427-7421.

June 19-21—**Family Practice Update.** USC at Pasadena Hilton Hotel, Pasadena. Fri-Sun. 16 hrs. $250. Contact: USC.

June 26—**Mucosal Injury, Esophageal Dysfunction, and Sleep Disorders.** Sequoia Hospital District, Redwood City. Fri. 7 hrs. $110. Contact: Daniel Liebowitz, MD, Sequoia Hospital, Whipple and Alameda, Redwood City 94062. (800) 345-0409.

June 28-29—**9th Annual Poison Control Center: Management of Drug Overdose and Poisoning.** UCSF at San Francisco. Sun-Mon. 14 hrs. $235. Contact: UCSF.

June 28-July 2—**Advances in Primary Care: 14th Annual Family Practice Refresher Course.** UCD at Caesar's Tahoe, So Lake Tahoe. Sun-Thurs. Contact: UCD.

June 30-July 6—**1987 Update on AIDS and Hepatitis: A Multidisciplinary Conference.** University of Hawaii at Royal Waikoloa Resort Hotel, The Big Island, Hawaii. Tues-Mon. 25 hrs. Contact: Stacey W. Grace, Program Director, Reed Research Institute, 250 Arapahoe Ave, Ste 303, Boulder, CO 80302. (800) 647-9593.

July 6-9—**Family Practice Board Review.** UCSF at UCSF. Mon-Thurs. 25 hrs. $375. Contact: UCSF.

August 16-26—**30th Anniversary Postgraduate Refresher Course—Program I.** USC at Sheraton Waikiki Hotel, Honolulu and the Marriott Hotel, Maui, Hawaii. Sun-Wed. 37 hrs. $535-585. Contact: USC, in California, (800) 321-1919, outside California, (800) 421-6729.

August 20-21—**6th Annual: General Medicine Update for Practicing Physicians.** Northern Inyo Hospital, Bishop. Wed-Thurs. 10 hrs. Contact: Lynda Schmidt, Northern Inyo Hosptial, 150 Pioneer Lane, Bishop 93514. (619) 873-5811.

August 23-September 2—**30th Anniversary Postgraduate Refresher Course—Program II.** USC at Marriott Hotel, Maui and the Waiohai Hotel, Kaui, Hawaii. Sun-Wed. 37 hrs. $535-585. Contact: USC, in California, (800) 321-1929, outside California, (800) 421-6729.

August 30—**1 Day Dermatology and Dermatologic Office Procedures Workshop.** Continuing Medical Education Associates at Newporter Resort, Newport Beach. Sun. 7 hrs. $195. Contact: J. Shiller, CMEA, PO Box 84296, San Diego 92138. (619) 223-2997.

September 9-11—**Primary Care Medicine: Principles and Practice.** UCSF at Hyatt on Union Square, San Francisco. Wed-Fri. $365. Contact: UCSF.

September 13—**1 Day Dermatology and Dermatologic Office Procedures Workshop.** Continuing Medical Education Associates at Holiday Inn Union Square, San Francisco. Sun. 7 hrs. $195. Contact: J. Shiller, CMEA, PO Box 84296, San Diego 92138. (619) 223-2997.

(Continued on Page 646)

# 95th ANNUAL MEETING

## IDAHO MEDICAL ASSOCIATION

July 29-August 1, 1987

Coeur d'Alene, Idaho

# AN INVITATION TO THE COEUR D'ALENE JULY 29-AUGUST 1, 1987

We are pleased to extend to you a cordial invitation to attend the 95th Annual Meeting of the Idaho Medical Association at the beautiful Coeur d'Alene Resort on the lake. An excellent scientific session has been planned that should appeal to all physicians. It should be a good opportunity not only to enjoy northern Idaho on one of the country's most beautiful lakes, but also receive 8 CME credit hours of Category I at an informative scientific session.

**JULIAN O. NICHOLSON, MD, PRESIDENT**
IDAHO MEDICAL ASSOCIATION

## 95th ANNUAL MEETING—IDAHO MEDICAL ASSOCIATION

### WEDNESDAY, JULY 29, 1987

**9 am to 5 pm** **HOUSE OF DELEGATES**

### THURSDAY, JULY 30
### SCIENTIFIC SESSION

**7:30 am** **BIOLOGIC CONTROL OF CANCER**
John Thompson, MD
University of Washington, Division of Oncology

**9:30 am** **CANCER PAIN**
George Khoury, MD
UCLA Cancer Pain Clinic, UCLA Anesthesiology Dept., Los Angeles, California

**11:00 am** **CURRENT STATUS OF VIRUS TREATMENT**
Ann Collier, MD
Harborview Medical Center, Seattle, Washington

**1:30 pm** **ALTERNATIVE THERAPIES**
Paul Wassermann, MD
Scottsdale Clinic, Division of Oncology

**2:30 pm** **WHERE ARE WE GAINING IN THE BATTLE AGAINST CANCER?**
John Thompson, MD

**3:30 pm** **SCREENING FOR CANCER, WHERE DOES IT PAY?**
Paul Wassermann, MD

### FRIDAY, JULY 31
### SCIENTIFIC SESSION

**8:30 am** **ONCOLOGIC IMAGING IN DIAGNOSIS AND STAGING**
Charles Carrasco, MD
St. Luke's Hospital, Boise, Idaho

**10:00 am** **MAMMOGRAPHIC SCREENING—IS IT WORTH THE TROUBLE?**
Jake Meighan, MD
Inland Imaging, Spokane, Washington

Father Bill Wassmuth, Chairman, Kootenai County Task Force on Human Relations, will address the IMA Auxiliary this morning

### SATURDAY, AUGUST 1

**8:30 am** **CLOSING SESSION, HOUSE OF DELEGATES**

**Registration Fee**—$150 for non-IMA members and out-of state physicians.
**For Information Contact:** Idaho Medical Association, PO Box 2668
Boise, ID 83701
Telephone: (208) 344-7888

# Accommodations at The Coeur d'Alene

The Coeur d'Alene offers a variety of accommodations and rates. Each room is designed for maximum comfort and convenience. The following is a brief description of our room types.

## LAKE TOWER

These oversized rooms are in our new 18-story Lakeside Tower. King or two double bed accommodations are available all with views of the Lake and surrounding mountains.

**Deluxe,** our finest rooms. Featuring separate living and dressing areas, balconies, refrigerators, and fireplaces. The views of the Lake are superb!

**Medium,** exceptional accommodations. Featuring separate living and dressing areas, balconies, refrigerators, and views of the Lake are very good.

**Standard,** our Lake Tower Standards are all excellent. Featuring separate living and dressing areas, refrigerators and views of the mountains.

## PARK TOWER

All rooms are newly remodeled and tastefully appointed.

**Deluxe,** offering two double bed accommodations with balconies and a westerly view of the Lake.

**Medium,** offering queen accommodations with an easterly view of the Lake or two double bed accommodations near our outdoor pool.

**Standard,** our most economical, queen accommodations overlooking our Sherman Avenue Park.

## SUITES

Honeymoon, family and executive suites available from 500 to 3,000 square feet. Prices available on request.

Preferred check-in after 3:00 p.m. Check-out time, 12:00 noon.

All rates subject to Idaho State and Lodging Taxes.

If your specific request cannot be honored, reservations will be made at the nearest available comparable room type and rate.

No charge for children under 18 staying in the same room with an adult.

All reservations must be accompanied by first night's deposit or guaranteed by a major credit card.

Cancellations must be received at least 24 hours in advance.

Airport limousine service is available at a nominal fee upon request with prior notification.

**TOLL FREE RESERVATIONS:**

**Continental U.S. . . 1 (800) 826-2390**

**Idaho . . . . . 1 (800) 841-5868**

**(208) 765-4000**

Name (Please Print)_____

Address _____

City _____ State _____ Zip _____

Telephone (_____) _____

Arrival (Date/Time) _____ Departure _____

No. in Party _____ Adults _____ Children (Under18) _____

Sharing room with _____

☐ I require limousine service from

☐ Spokane Airport ☐ Couer D'Alene Airport

Airline _____ Flt. No. _____ Arr. Time _____

☐ I will be arriving by automobile and will require parking

I am attending

Idaho Medical Association 95th Annual Meeting

Dates: JULY 29-AUGUST 1

Please check single or double and room preference:

### LAKE TOWER

☐ King
☐ Two Dble Beds

| | Single | Double |
|---|---|---|
| Deluxe | ☐ $89.50 | ☐ $89.50 |
| Medium | ☐ 79.50 | ☐ 79.50 |
| Standard | ☐ 74.50 | ☐ 74.50 |

For third and fourth adult (age 18 and over) in the same room, add $10 per person to prices shown

### PARK TOWER

☐ Queen
☐ Two Dble Beds

| | Single | Double |
|---|---|---|
| Deluxe | ☐ $69.50 | ☐ $69.50 |
| Medium | ☐ 64.50 | ☐ 64.50 |
| Standard | ☐ 59.50 | ☐ 59.50 |

For third and fourth adult (age 18 and over) in the same room, add $10 per person to prices shown

### SUITES

☐ Please send information on your suites and hospitality rooms.

☐ Deposit Included: Amount $_____

☐ Charge My Credit Card ☐ Visa ☐ Mastercard ☐ American Express

_____ / _____

Card Number Expiration Date

_____

Signature

To assure room availability, reservations must be made 30 days before your meeting.

**PLEASE RETURN FORM WITH DEPOSIT TO: THE COEUR D'ALENE**
**ATTN: Reservations**
**On-The-Lake**
**Coeur d'Alene, Idaho 83814**

MKT: 186B

CONTINUING MEDICAL EDUCATION

(Continued from Page 642)

September 14-18—**STD Clinician Training Course—Intensive.** Long Beach Health Dept. Mon-Fri. Contact: Anne-Renee Heningberg, Long Beach STD Training Center, PO Box 6157, Long Beach 90806. (213) 427-7421.

September 20—**1 Day Dermatology and Dermatologic Office Procedures Workshop.** Continuing Medical Education Associates at Hyatt Islandia Hotel, San Diego. Sun. 7 hrs. $195. Contact: J. Shiller, CMEA, PO Box 84296, San Diego 92138. (619) 223-2997.

September 21-22—**7th Annual Bristol-Myers Symposium on Nutrition Research: Nutrition and the Origins of Disease.** UCD at Fairmont Hotel, San Francisco. Mon-Tues. Contact: UCD.

October 16-18—**Office Orthopedics for the Primary Care Physician.** Sharp Memorial Hospital at San Diego Princess Hotel. Fri-Sun. 20 hrs. $365. Contact: J. Shiller, CMEA, PO Box 84296, San Diego 92138. (619) 223-2997.

October 19-22—**Annual Family Practice Update.** Mon-Thurs. LLU at LLU. Contact: LLU.

October 19-30—**Sexually Transmitted Disease (STD) Clinician Training Course—Comprehensive.** Long Beach Health Department and UCI at Long Beach. Mon-Fri. Anne-Renee Heningberg, Long Beach STD Training Center, PO Box 6157, Long Beach 90806. (213) 427-7421.

October 26-November 1—**Traumatic Brain Injury.** UCD at Red Lion Motor Inn, Sacramento. Mon-Sun. Contact: UCD.

## IDAHO

June 28-July 5—**Effective Management of Common Sports Injuries.** Middle Fork of the Salmon River. One week. Sponsored by the University of Arizona College of Medicine, Department of Family and Community Medicine, and Epic Expeditions. 24 hrs. Contact: Kathy Rairigh, EPIC EXPEDITIONS, PO Box 209, Sun Valley, ID 83353. (208) 788-4995.

July 27-August 2—**Idaho Medical Association Annual Meeting.** Coeur d'Alene. One week. Contact: IMA, 305 W Jefferson, PO Box 2668, Boise 83701. (208) 344-7888.

August 1-8—**Forefronts in Pediatrics.** Sun Valley. One week. Sponsored by the University of Arizona College of Medicine, Department of Family and Community Medicine, and Epic Expeditions. 24 hrs. Contact: Kathy Rairigh, EPIC EXPEDITIONS, PO Box 209, Sun Valley, ID 83353. (208) 788-4995.

August 13-15—**Sun Valley Emergency Medical Conference.** Convention Center, Sun Valley. Thurs-Sat. Contact: Idaho EMS System, 450 W State St, Boise 83720. (208) 334-5994.

## MONTANA

June 18-20—**Montana Academy of Family Physicians—Annual Meeting.** Fairmont Hot Springs, Anaconda. 17 hrs. Contact: John Patterson, MD, 7 E Beall, Bozeman 59715. (406) 587-5123.

## NEW MEXICO

Information, requests for accreditation and items to be listed should be sent to the chairman of the CME Committee, New Mexico Medical Society, 303 San Mateo NE, Suite 204, Albuquerque, NM 87108 at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 266-7868.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

May 15-16—**Biological and Ethical Dimensions of Human Transplantation.** Albuquerque. Fri-Sat. Contact: Office of Medical Education, Presbyterian Hospital, PO Box 26666, Albuquerque 87125. (505) 841-1225.

June 12-13—**Dermatology in the Primary Care Setting.** Albuquerque. Fri-Sat. VA Medical Center. Contact: Office of Continuing Medical Education, UNM School of Medicine, Albuquerque 87131. (505) 277-3942.

June 25-27—**General Surgical Update.** Albuquerque. Thurs-Sat. Marriott Hotel. Contact: Office of Continuing Medical Education, UNM School of Medicine, Albuquerque 87131. (505) 277-3942.

June 23-28—**New Mexico Osteopathic Medical Association Annual Meeting.** Albuquerque. Tues-Sun. Pyramid Hotel. Contact: NMOMA, PO Box 3096, Albuquerque 87110. (505) 884-0201.

July 9-11—**New Mexico Ophthalmological Society Annual Meeting.** Santa Fe. Thurs-Sat. Contact: John Mezoff, MD, PO Box 1959, Gallup 87301. (505) 722-2268.

July 20-23—**New Mexico Chapter, American Academy of Family Physicians.** Ruidoso. Inn of the Mountain Gods. Mon-Thurs. Contact: NM Chapter, AAFP, PO Box 23070, Albuquerque 87192. (505) 298-5300.

July 24-25—**Santa Fe Cardiology Symposium.** Santa Fe. Fri-Sat. Contact: Richard D. Lueker, MD, 909 Virginia NE, #202, Albuquerque 87108. (505) 255-8474.

September 24-26—**Wilson Lectureship.** Albuquerque. Thurs-Sat. Contact: Presbyterian Heart Institute Cardiology Symposium, PO Box 26666, Albuquerque 87125. (505) 841-1065.

## UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the CME office of the Utah State Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. They also must meet the definition of Utah Approved CME Credit for the purpose of medical license reregistration in Utah. Accredited institutions wishing to list AMA Category 1/Utah Approved CME courses here should send information at least two months in advance to the Office of Continuing Medical Education, 540 East Fifth South, Salt Lake City, Utah 84102; or phone (801) 355-5290. For information on CME accreditation or on the CME requirements of the Utah Physicians' Licensing Board, please write the CME office at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution or the CME office for current details.

### MEDICAL GRAND ROUNDS

Each Wed—8:00-9:00 a.m. Alternating between University of Utah Medical Center and VA Medical Center, Salt Lake City. Contact: William D. Odell, MD, PhD, Professor and Chairman, Dept of Internal Medicine, Univ of Utah, (801) 581-7606.

(Continued on Page 648)

# Classified Advertisements

The rate for each insertion is **$6 per line** (average six words per line) **with five line ($30) minimum.** Box number charge: $5 each month.

**Classified display rates $50 per inch.**

Copy for classified advertisements should be received not later than **25th of the second month preceding issue. All copy must be typed or printed.** • Classified advertisers using Box Numbers forbid the disclosure of their identity; your inquiries in writing will be forwarded to Box Number advertisers. The right is reserved to reject or modify all classified advertising copy in conformity with the decisions of the Advertising Committee.

**Please Type or Print Advertising Copy**

## Classified Advertisements Are Payable in Advance

CLASSIFIED ADVERTISEMENTS
THE WESTERN JOURNAL OF MEDICINE
P.O. BOX 7602, SAN FRANCISCO, CA 94120-7602

### PHYSICIANS WANTED

**ARIZONA BASED PHYSICIAN RECRUITMENT** firm has opportunities Coast to Coast. "Professionals working with Professionals." Over 14 years experience. Call (602) 990-8080; or send CV to: Mitchell & Associates, Inc., PO Box 1804, Scottsdale, AZ 85252.

**ARIZONA EMERGENCY MEDICINE:** An emergency department Medical Directorship and staff positions are immediately available at two client hospitals located in Kingman and Lake Havasu City. Moderate volume emergency departments. Excellent nursing and medical staff support. We offer a guaranteed competitive rate of compensation, occurrence malpractice insurance coverage, CME allowance, reimbursement of professional dues. Directors also receive paid health benefits which include dependents. For additional information contact Bill Salmo, Spectrum Emergency Care, 6275 Lehman Dr., Ste C-202, Colorado Springs, CO 80918; 1 (800) 525-3681; (303) 590-1755.

**FULL-TIME BOARD CERTIFIED FAMILY PRACTITIONER** sought by 8-physician department of Family Practice in 70-physician multispecialty group. No obstetrics. Full medical services available. Woodland is near Sacramento, 1½ hours from San Francisco and 2 hours from Lake Tahoe. Send CV to Michael Pirruccello, MD, 1207 Fairchild Court, Woodland, CA 95695; (916) 666-2466.

**CALIFORNIA:** An excellent opportunity is currently available to join team of physicians providing emergency department coverage at full service community hospital. Located in beautiful Redwood area of northern California. Guaranteed competitive rate of compensation, occurrence malpractice insurance coverage, allowance for CME, reimbursement of professional dues. For additional information on this opportunity contact Bill Salmo, Spectrum Emergency Care, 6275 Lehman Dr., Ste. C-202, Colorado Springs, CO 80918; 1 (800) 525-3681; (303) 590-1755.

**INTERNIST—BE/BC.** Recently trained. Send CV to: San Diego Heart & Medical Clinic, 3660 Clairemont Dr., Suite 6, San Diego, CA 91117; or call J. Kleid, MD (619) 274-2560.

**ORTHOPEDIC SURGEON.** F/T Orthopedic Surgeon to join growing multispecialty group in southern California. Salary plus malpractice and benefits. Great potential for right physician; individual ownership. Send CV to Number 18, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

### PHYSICIANS WANTED

**PHYSICIANS WANTED.** Physicians, BC/BE needed immediately to join expanding multispecialty group. Practice in rapidly growing Southwest community (population 500,000+). Fee-for-service and prepaid health care. Group includes Family Practice/Pediatrics, Internal Medicine/Subspecialties/24 hour Urgent Care. Teaching appointment. Position offers excellent compensation and benefits plus full pension and profit sharing. Relocation expenses. Interested individuals should reply with curriculum vitae to: Southwest Medical Associates, 333 N. Rancho Dr., Ste. 100, Las Vegas, NV 89106.

**SAN DIEGO, CALIFORNIA.** Exciting ground floor opportunities for physicians in primary care/ambulatory GYN (no OB) in provision of health care exclusively to women. Quality feminine surroundings. Salary plus incentive and malpractice coverage. Send CV to Centers for Women's Medicine Medical Group, 701 "B" Street, Ste. 330-WJM, San Diego, CA 92101.

**VICE PRESIDENT MEDICAL SERVICES.** Offers challenging opportunity to systems oriented physician for Prepaid Health Plan and fee for service medical center(s). Excellent salary and fringe benefits. Requires California Medical License; one year of formal training in health administration or two years experience in medical care management and proficiency in primary clinical care. Please submit Curriculum Vitae to James M. Clayton, CEO, FHFA, PO Box 30051, San Jose, CA 95156-9985. EOE.

**OREGON**—General Internist sought for busy practice. Multispecialty group of 10 physicians, 38 miles from Portland. CV to Administrator, Physicians' Medical Center, P.C., 420 East Fifth St., McMinnville, OR 97128; phone (503) 472-6161.

**NEAR STANFORD**—Six Internists, all sub-specialty trained and members of clinical faculty at Stanford, interested in an Associate with subspecialty interest and training. Should be well grounded in Internal Medicine. Send CV to: Dr. Bigler, El Camino Internal Medical Group, 125 South Dr., Mountain View, CA 94040.

**WASHINGTON—PUGET SOUND AREA.** Six person Family Practice Group in multispecialty clinic has opening for two BE/BC Family Practitioners. Obstetrics encouraged. Excellent practice opportunity with full range of fringe benefits. Please reply with CV to: William A. Latta, Administrator, 500 N. Lilly Rd., Olympia, WA 98506; (206) 456-1122.

### PHYSICIANS WANTED

**ADDITIONAL INTERNIST NEEDED** for busy five physician multispecialty group. Beautiful, well-equipped six year old office just 75 feet from 34-bed hospital with ICU/CCU unit. This all Board certified group houses three Family Practitioners, two General Surgeons, and one Internist. Coastal retirement town offers top notch school system and excellent array of activities. Located just 75 easy miles from Portland adds even more cultural and shopping opportunities. For further information contact Rick Bigger days at North Coast Medical Center, P.C., Seaside, Oregon; (503) 738-9551.

**NORTHERN CALIFORNIA:** FP/IM physicians needed to staff ambulatory care clinics in the Central Valley region of California. Paid malpractice and excellent benefit package. Incentive plus guarantee. If interested, please contact SEMG, PO Box 214584, Sacramento, CA 95821.

**SEATTLE AREA**—Neurologist, Orthopedist, ENT, wanted for multispecialty clinic in beautiful seaside community. Excellent lifestyle in growing area. Expense sharing with established group in new facility allows clinical practice without administrative demands. Reply with CV to: North Kitsap Medical Center, 20700 Bond Rd. N.E., Poulsbo, WA 98370.

**INTERNIST BC/BE**—Busy internal medicine/endocrinology group practice in central California seeks Internist to join. New graduates encouraged. Reply with CV to: PO Box 5716, Fresno, CA 93755-5716.

**PEDIATRICIAN BC/BE** for hospital-based teaching practice. Interest and training in neonatology and critical care pediatrics preferred. Join two full-time pediatricians and two full-time neonatologists in hospital with Level II ICN and busy inpatient and out-patient services. Paid malpractice. Salary negotiable based on training and experience. Submit CV and references to: Patricia A. Dixon, MD, Director, Pediatrics/Neonatal Services, San Joaquin General Hospital, PO Box 1020, Stockton, CA 95201; (209) 468-6600. AA/EOE.

**OREGON COAST:** Wanted BC/BE Family Practice physician to join five FPs in multispecialty group. OB included. Contact Kent Sharman, MD, at North Bend Medical Center, Inc., 1900 Woodland Dr., Coos Bay, OR 97420 or call (503) 267-5151 or (within Oregon) (800) 452-5863.

**PHYSICIAN—INTERNAL MEDICINE** needed to join Christian interdisciplinary health care team serving the whole person in community. Exciting, growing regional oncology and preventive medicine institute. Person must be traditionally trained, Board certified or eligible, have broad experience and interest in complimentary therapies. State-of-the-art equipment. Competitive salary commensurate with experience and training. Contact Dr Kenneth Bakken, Executive Director, Northwest Oncology Clinics, 901 Boren Ave., Ste. 901, Seattle, WA 98104; telephone (206) 292-2277.

## PHYSICIANS

Excellent immediate medical opportunities. Physicians needed full- or part-time to staff hospital owned system of successful urgent care center open 12 hours daily. U.S. Medical School and FP or Internal Medicine residency training desired, BC/BE required. Strong career growth, salary plus incentive and excellent benefits, malpractice insurance paid. Close to skiing, national parks and recreational areas. Please call (801) 321-2490 or send CV to: Bruce Harrow, MD, 55 North Redwood Rd., Salt Lake City, UT 84116. Equal Opportunity Employer, M/F/H/V.

*(Continued on Page 651)*

CONTINUING MEDICAL EDUCATION

*(Continued from Page 646)*

June 11-13—**Annual Castle Country Rural Medical Symposium** (Sponsor: Carbon County Medical Society). Thurs-Sat. Raddison Inn, Price. 14 hrs. Contact: Mary Ghardelli, (801) 637-4800, ext 203.

September 9-11—**Utah State Medical Association Annual Meeting.** Marriott Hotel, Salt Lake City. Wed-Fri. Contact: USMA, 540 E Fifth South, Salt Lake City 84102. (801) 355-5290.

### SPONSORS OF COURSES—ABBREVIATIONS

AHA: American Heart Association, Utah Affiliate, 645 E 400 South, Salt Lake City 84102. (801) 322-5601.

BYUHS: Brigham Young University Health Services, McDonald Student Health Center, Brigham Young University, Provo 84602. (801) 378-2771.

CH: Castleview Hospital (formerly Carbon Hospital), RFD 2, Box 46, Price 84501. (801) 637-4800.

CWH: Cottonwood Hospital, 5770 S 300 East, Salt Lake City 84101. (801) 262-3461.

DMC: Dixie Medical Center, 544 S 400 East, St George 84770. (801) 673-9681.

HCH: Holy Cross Hospital, 1045 E First South, Salt Lake City 84102. (801) 350-4744.

ITS: Intermountain Thoracic Society, 1616 S 11th East, Salt Lake City 84105. (801) 484-4456.

LDSH: Latter-Day Saints Hospital, 325 8th Ave, Salt Lake City 84143. (801) 350-1100.

LRH: Logan Regional Hospital, 1400 N 5th East, Logan 84321. (801) 752-2050.

MDH: McKay-Dee Hospital Center, 3939 Harrison Blvd, Ogden 84409. (801) 399-4141.

MVH: Mountain View Hospital, 1000 E Highway 6, Payson 84651. (801) 465-9201.

144: 144th Evacuation Hospital, PO Box 8000, Salt Lake City 84108. (801) 524-3924.

OSS: Ogden Surgical Society, PO Box 9311, Ogden 84409.

PCMC: Primary Children's Medical Center, 320 12th Ave, Salt Lake City 84103. (801) 363-1221.

PVH: Pioneer Valley Hospital, 3460 S 4155 West, West Valley City 84120. (801) 968-9061.

SMH: St Mark's Hospital, 1200 E 3900 South, Salt Lake City 84117. (801) 268-7111.

UOS: Utah Ophthalmological Society, 540 E 500 South, Salt Lake City 84102. (801) 355-7477.

USH: Utah State Hospital, PO Box 270, Provo 84603-0270. (801) 373-4400.

UUMC: University of Utah Medical Center, 50 N Medical Dr, Salt Lake City 84132. (801) 581-2258.

UVH: Utah Valley Hospital, 1034 N Fifth West, Provo 84601. (801) 373-7850.

VAMC: Veterans Administration Medical Center, 500 Foothill Dr, Salt Lake City 84148. (801) 582-1565.

VVMC: Valley View Medical Center, 595 S 75 East, Cedar City 84720. (801) 586-6587.

## WASHINGTON

This listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. To list Category 1 programs here please send information at least two months in advance to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 900, Seattle, WA 98121; or phone (206) 441-WSMA.

Brochures and registration forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

May 15—**Office Gynecology for the Primary Care Physician.** Seattle. Fri. Virginia Mason Medical Center. Contact: VMMC.

May 20—**Management of Benign and Malignant Breast Disease.** Seattle. Wed. U/W Health Sciences. Contact: U/W.

May 27—**Dermatology.** Seattle. Wed. Gould Auditorium, Northwest Hospital. Contact: (206) 364-0500, #1621.

May 28-29—**Workers Compensation Update.** Seattle. Thurs-Fri. NW Center for Occupational Health and Safety. Contact U/W.

June 3—**Flexible Sigmoidoscopy III or IV.** Seattle. Wed. Gould Auditorium, Northwest Hospital. Contact: (206) 364-0500, #1621.

June 17-19—**Family Violence.** Seattle. Wed-Fri. Kane Hall, U/W. Contact: U/W.

June 25-26—**Infectious Diseases.** Seattle. Thurs-Fri. Holiday Inn Crowne Plaza. Contact: (206) 364-0500, #1621.

July 19-23—**Reducing Risks From Environmental Chemicals Through Biotechnology.** Seattle. Sun-Thurs. NW Center for Occupational Health and Safety. Contact: U/W.

July 24-26—**WSSA: Seafair IX Regional Anesthesia.** Seattle. Fri-Sun. Virginia Mason Medical Center. Contact: VMMC.

### COURSE SPONSORS AND CONTACT INFORMATION

CME HARBORVIEW—Contact: Gayle Splater, Cytology Continuing Education, Dept. of Pathology, Harborview Medical Center, 325 Ninth Avenue, Seattle, WA 98104. (206) 223-5953.

CME PIERCE COUNTY—Contact: Mrs Maxine Bailey, Executive Director, College of Medical Education, 705 South Ninth, No. 203, Tacoma, WA 98405. (206) 627-7137.

U/W (UNIVERSITY OF WASHINGTON)—Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

WSMA—Washington State Medical Association, Continuing Medical Education, 2033 Sixth Ave, Suite 900, Seattle, WA 98121. (206) 441-9762.

VMMC (VIRGINIA MASON MEDICAL CENTER)—Contact: Linda Orgel, Division of Continuing Medical Education, Virginia Mason Medical Center, PO Box 900, Seattle, WA 98111. (206) 223-6898.

## WYOMING

June 25-29—**Wyoming Medical Society Annual Meeting.** Jackson Lake Lodge, Moran. Thurs-Mon. Contact: WMS, PO Drawer 4009, Cheyenne 82003-4009. (307) 635-2424.

June 28-July 2—**Update on General Pediatrics.** University of Nebraska College of Medicine at Jackson Hole Racquet Club, Jackson. Sun-Thurs. Contact: Brenda Ram, Center for Continuing Education, Univ of Nebraska Medical Center, 42nd and Dewey Ave, Omaha, NE 68105. (402) 559-4152.

July 5-9—**Sports Medicine Update 1987.** University of Nebraska College of Medicine at Jackson Hole Racquet Club, Jackson. Sun-Thurs. Contact: Brenda Ram, Center for Continuing Education, Univ of Nebraska Medical Center, 42nd and Dewey Ave, Omaha, NE 68105. (402) 559-4152. ◆

# DEPAKOTE®

## DIVALPROEX SODIUM ENTERIC-COATED TABLETS

**All the advantages of Depakene® (valproic acid) plus improved gastrointestinal tolerance**

# NOW ON MEDI-CAL FORMULARY

Medi-Cal Numbers:

(Actual size)

500 mg

**2414D**
**500 mg**

(Actual size)

250 mg

**2414A**
**250 mg**

(Actual size)

125 mg

NO. PENDING
**125 mg**

Please see adjoining page for prescribing information.

Abbott Laboratories, North Chicago, IL60064

# DEPAKOTE®

## DIVALPROEX SODIUM
## ENTERIC-COATED TABLETS

## NOW ON MEDI-CAL FORMULARY

**WARNING:**
HEPATIC FAILURE RESULTING IN FATALITIES HAS OCCURRED IN PATIENTS RECEIVING VALPROIC ACID AND ITS DERIVATIVES. EXPERIENCE HAS INDICATED THAT CHILDREN UNDER THE AGE OF TWO YEARS ARE AT A CONSIDERABLY INCREASED RISK OF DEVELOPING FATAL HEPATOTOXICITY, ESPECIALLY THOSE ON MULTIPLE ANTICONVULSANTS, THOSE WITH CONGENITAL METABOLIC DISORDERS, THOSE WITH SEVERE SEIZURE DISORDERS ACCOMPANIED BY MENTAL RETARDATION, AND THOSE WITH ORGANIC BRAIN DISEASE. WHEN DEPAKOTE IS USED IN THIS PATIENT GROUP, IT SHOULD BE USED WITH EXTREME CAUTION AND AS A SOLE AGENT. THE BENEFITS OF SEIZURE CONTROL SHOULD BE WEIGHED AGAINST THE RISKS. ABOVE THIS AGE GROUP, EXPERIENCE HAS INDICATED THAT THE INCIDENCE OF FATAL HEPATOTOXICITY DECREASES CONSIDERABLY IN PROGRESSIVELY OLDER PATIENT GROUPS.
THESE INCIDENTS USUALLY HAVE OCCURRED DURING THE FIRST SIX MONTHS OF TREATMENT. SERIOUS OR FATAL HEPATOTOXICITY MAY BE PRECEDED BY NON-SPECIFIC SYMPTOMS SUCH AS LOSS OF SEIZURE CONTROL, MALAISE, WEAKNESS, LETHARGY, FACIAL EDEMA, ANOREXIA AND VOMITING. PATIENTS SHOULD BE MONITORED CLOSELY FOR APPEARANCE OF THESE SYMPTOMS. LIVER FUNCTION TESTS SHOULD BE PERFORMED PRIOR TO THERAPY AND AT FREQUENT INTERVALS THEREAFTER, ESPECIALLY DURING THE FIRST SIX MONTHS.

**DESCRIPTION:** Divalproex sodium is a stable coordination compound comprised of sodium valproate and valproic acid in a 1:1 molar relationship and formed during the partial neutralization of valproic acid with 0.5 equivalent of sodium hydroxide. Chemically it is designated as sodium hydrogen bis(2-propylpentanoate).

Divalproex sodium has a molecular weight of 310.41 and occurs as a white powder with a characteristic odor.

DEPAKOTE is an oral antiepileptic supplied as enteric-coated tablets in three dosage strengths containing divalproex sodium equivalent to 125 mg, 250 mg or 500 mg of valproic acid.

**Inactive Ingredients**
125 mg tablets: cellulosic polymers, diacetylated monoglycerides, FD&C Blue No. 1, FD&C Red No. 40, povidone, pregelatinized starch (contains corn starch), silica gel, talc, titanium dioxide, vanillin and other ingredients.

250 mg tablets: cellulosic polymers, diacetylated monoglycerides, FD&C Yellow No. 6, iron oxide, povidone, pregelatinized starch (contains corn starch), silica gel, talc, titanium dioxide, vanillin and other ingredients.

500 mg tablets: cellulosic polymers, diacetylated monoglycerides, D&C Red No. 30, FD&C Blue No. 2, iron oxide, povidone, pregelatinized starch (contains corn starch), silica gel, talc, titanium dioxide, vanillin and other ingredients.

**CLINICAL PHARMACOLOGY:** DEPAKOTE is an antiepileptic agent which is chemically related to valproic acid. It has no nitrogen or aromatic moiety characteristic of other antiepileptic drugs. The mechanism by which DEPAKOTE exerts its antiepileptic effects has not been established. It has been suggested that its activity is related to increased brain levels of gamma-aminobutyric acid (GABA). The effect on the neuronal membrane is unknown. DEPAKOTE dissociates into valproate in the gastrointestinal tract.

Because of the enteric coating of DEPAKOTE, absorption is delayed one hour following oral administration. Thereafter, DEPAKOTE is uniformly and reliably absorbed, as shown by studies in normal volunteers. Peak serum levels of valproate occur in 3 to 4 hours. Bioavailability of divalproex sodium tablets was found to be equivalent to that of DEPAKENE® (valproic acid) capsules. Concomitant administration with food would be expected to slow absorption but not affect the extent of absorption. The serum half life of valproate is typically in the range of six to sixteen hours. Half-lives in the lower part of the above range are usually found in patients taking other antiepileptic drugs capable of enzyme induction.

Enteric-coated divalproex sodium may reduce the incidence of the irritative gastrointestinal effects of valproate as compared to valproic acid capsules.

Valproate is rapidly distributed and at therapeutic drug concentrations, drug is highly bound (90%) to human plasma proteins. Increases in dose may result in decreases in the extent of protein binding and increased valproate clearance and elimination.

Elimination of DEPAKOTE and its metabolites occurs principally in the urine, with minor amounts in the feces and expired air. Very little unmetabolized parent drug is excreted in the urine. The drug is primarily metabolized in the liver and is excreted as the glucuronide conjugate. Other metabolites in the urine are products of beta, omega-1, and omega-oxidation (C-3, C-4 and C-5 positions). The major oxidative metabolite in the urine is 2-propyl-3-keto-pentanoic acid; minor metabolites are 2-propyl-glutaric acid, 2-propyl-5-hydroxypentanoic acid, 2-propyl-3-hydroxypentanoic acid and 2-propyl-4-hydroxypentanoic acid.

**INDICATIONS AND USAGE:** DEPAKOTE (divalproex sodium) is indicated for use as sole and adjunctive therapy in the treatment of simple (petit mal) and complex absence seizures. DEPAKOTE may also be used adjunctively in patients with multiple seizure types which include absence seizures.

In accordance with the International Classification of Seizures, simple absence is defined as very brief clouding of the sensorium or loss of consciousness (lasting usually 2-15 seconds), accompanied by certain generalized epileptic discharges without other detectable clinical signs. Complex absence is the term used when other signs are also present.

SEE "WARNINGS" SECTION FOR STATEMENT REGARDING FATAL HEPATIC DYSFUNCTION.

**CONTRAINDICATIONS:** DEPAKOTE (DIVALPROEX SODIUM) SHOULD NOT BE ADMINISTERED TO PATIENTS WITH HEPATIC DISEASE OR SIGNIFICANT DYSFUNCTION.

DEPAKOTE is contraindicated in patients with known hypersensitivity to the drug.

**WARNINGS: Hepatic failure resulting in fatalities has occurred in patients receiving valproic acid. These incidents usually have occurred during the first six months of treatment. Serious or fatal hepatotoxicity may be preceded by non-specific symptoms such as loss of seizure control, malaise, weakness, lethargy, facial edema, anorexia and vomiting. Patients should be monitored closely for appearance of these symptoms. Liver function tests should be performed prior to therapy and at frequent intervals thereafter, especially during the first six months. However, physicians should not rely totally on serum biochemistry since these tests may not be abnormal in all instances, but should also consider the results of careful interim medical history and physical examination. Caution should be observed when administering DEPAKOTE to patients with a prior history of hepatic disease. Patients on multiple anticonvulsants, children, those with congenital metabolic disorders, those with severe seizure disorders accompanied by mental retardation, and those with organic brain disease may be at particular risk. Experience has indicated that children under the age of two years are at a considerably increased risk of developing fatal hepatotoxicity, especially those with the aforementioned conditions. When DEPAKOTE is used in this patient group, it should be used with extreme caution and as a sole agent. The benefits of seizure control should be weighed against the risks. Above this age group, experience has indicated that the incidence of fatal hepatotoxicity decreases considerably in progressively older patient groups.**

**The drug should be discontinued immediately in the presence of significant hepatic dysfunction, suspected or apparent. In some cases, hepatic dysfunction has progressed in spite of discontinuation of drug.**

The frequency of adverse effects (particularly elevated liver enzymes) may be dose related. The benefit of improved seizure control which may accompany the higher doses should therefore be weighed against the possibility of a greater incidence of adverse effects.

*Usage in Pregnancy:* ACCORDING TO PUBLISHED AND UNPUBLISHED REPORTS, VALPROIC ACID MAY PRODUCE TERATOGENIC EFFECTS IN THE OFFSPRING OF HUMAN FEMALES RECEIVING THE DRUG DURING PREGNANCY.

THERE ARE MULTIPLE REPORTS IN THE CLINICAL LITERATURE WHICH INDICATE THAT THE USE OF ANTIEPILEPTIC DRUGS DURING PREGNANCY RESULTS IN AN INCREASED INCIDENCE OF BIRTH DEFECTS IN THE OFFSPRING. ALTHOUGH DATA ARE MORE EXTENSIVE WITH RESPECT TO TRIMETHADIONE, PARAMETHADIONE, PHENYTOIN AND PHENOBARBITAL, REPORTS INDICATE A POSSIBLE SIMILAR ASSOCIATION WITH THE USE OF OTHER ANTIEPILEPTIC DRUGS. THEREFORE, ANTIEPILEPTIC DRUGS SHOULD BE ADMINISTERED TO WOMEN OF CHILDBEARING POTENTIAL ONLY IF THEY ARE CLEARLY SHOWN TO BE ESSENTIAL IN THE MANAGEMENT OF THEIR SEIZURES.

THE INCIDENCE OF NEURAL TUBE DEFECTS IN THE FETUS MAY BE INCREASED IN MOTHERS RECEIVING VALPROATE DURING THE FIRST TRIMESTER OF PREGNANCY. THE CENTERS FOR DISEASE CONTROL (CDC) HAS ESTIMATED THE RISK OF VALPROIC ACID EXPOSED WOMEN HAVING CHILDREN WITH SPINA BIFIDA TO BE APPROXIMATELY 1 TO 2%.[1] THIS RISK IS SIMILAR TO THAT FOR NONEPILEPTIC WOMEN WHO HAVE HAD CHILDREN WITH NEURAL TUBE DEFECTS (ANENCEPHALY AND SPINA BIFIDA).

ANIMAL STUDIES ALSO HAVE DEMONSTRATED VALPROIC ACID INDUCED TERATOGENICITY. Studies in rats and human females demonstrated placental transfer of the drug. Doses greater than 65 mg/kg/day given to pregnant rats and mice produced skeletal abnormalities in the offspring, primarily involving ribs and vertebrae; doses greater than 150 mg/kg/day given to pregnant rabbits produced fetal resorptions and (primarily) soft tissue abnormalities in the offspring. In rats a dose-related delay in the onset of parturition was noted. Postnatal growth and survival of the progeny were adversely affected, particularly when drug administration spanned the entire gestation and early lactation period.

Antiepileptic drugs should not be discontinued in patients in whom the drug is administered to prevent major seizures because of the strong possibility of precipitating status epilepticus with attendant hypoxia and threat to life. In individual cases where the severity and frequency of the seizure disorder are such that the removal of medication does not pose a serious threat to the patient, discontinuation of the drug may be considered prior to and during pregnancy, although it cannot be said with any confidence that even minor seizures do not pose some hazard to the developing embryo or fetus.

The prescribing physician will wish to weigh these considerations in treating or counseling epileptic women of childbearing potential.

**PRECAUTIONS:** *Hepatic Dysfunction:* See "Boxed Warning," "Contraindications" and "Warnings" sections.

*General:* Because of reports of thrombocytopenia, inhibition of the secondary phase of platelet aggregation, and abnormal coagulation parameters, platelet counts and coagulation tests are recommended before initiating therapy and at periodic intervals. It is recommended that patients receiving DEPAKOTE (divalproex sodium) be monitored for platelet count and coagulation parameters prior to planned surgery. Evidence of hemorrhage, bruising or a disorder of hemostasis/coagulation is an indication for reduction of DEPAKOTE dosage or withdrawal of therapy.

Hyperammonemia with or without lethargy or coma has been reported and may be present in the absence of abnormal liver function tests. If clinically significant elevation occurs, DEPAKOTE should be discontinued.

Since DEPAKOTE (divalproex sodium) may interact with concurrently administered antiepileptic drugs, periodic serum level determinations of concomitant antiepileptic drugs are recommended during the early course of therapy. (See "Drug Interactions" section.)

Valproate is partially eliminated in the urine as a keto metabolite which may lead to a false interpretation of the urine ketone test.

There have been reports of altered thyroid function tests associated with valproate. The clinical significance of these is unknown.

*Information for Patients:* Since DEPAKOTE may produce CNS depression, especially when combined with another CNS depressant (e.g., alcohol), patients should be advised not to engage in hazardous occupations, such as driving an automobile or operating dangerous machinery, until it is known that they do not become drowsy from the drug.

*Drug Interactions:* Valproic acid may potentiate the CNS depressant activity of alcohol.

The concomitant administration of valproic acid with drugs that exhibit extensive protein binding (e.g., aspirin, carbamazepine, and diclofenac) may result in alteration of serum drug levels.

THERE IS EVIDENCE THAT VALPROIC ACID CAN CAUSE AN INCREASE IN SERUM PHENOBARBITAL LEVELS BY IMPAIRMENT OF NON-RENAL CLEARANCE. THIS PHENOMENON CAN RESULT IN SEVERE CNS DEPRESSION. THE COMBINATION OF VALPROIC ACID AND PHENOBARBITAL HAS ALSO BEEN REPORTED TO PRODUCE CNS DEPRESSION WITHOUT SIGNIFICANT ELEVATIONS OF BARBITURATE OR VALPROATE SERUM LEVELS. ALL PATIENTS RECEIVING CONCOMITANT BARBITURATE THERAPY SHOULD BE CLOSELY MONITORED FOR NEUROLOGICAL TOXICITY. SERUM BARBITURATE LEVELS SHOULD BE OBTAINED, IF POSSIBLE, AND THE BARBITURATE DOSAGE DECREASED, IF APPROPRIATE.

Pyrimidone is metabolized into a barbiturate and, therefore, may also be involved in a similar or identical interaction.

THERE HAVE BEEN REPORTS OF BREAKTHROUGH SEIZURES OCCURRING WITH THE COMBINATION OF VALPROIC ACID AND PHENYTOIN. MOST REPORTS HAVE NOTED A DECREASE IN TOTAL PLASMA PHENYTOIN CONCENTRATION. HOWEVER, INCREASES IN TOTAL PHENYTOIN SERUM CONCENTRATION HAVE BEEN REPORTED. AN INITIAL FALL IN TOTAL PHENYTOIN LEVELS WITH SUBSEQUENT INCREASE IN PHENYTOIN LEVELS HAS ALSO BEEN REPORTED. IN ADDITION, A DECREASE IN TOTAL SERUM PHENYTOIN WITH AN INCREASE IN THE FREE VS. PROTEIN BOUND PHENYTOIN LEVELS HAS BEEN REPORTED. THE DOSAGE OF PHENYTOIN SHOULD BE ADJUSTED AS REQUIRED BY THE CLINICAL SITUATION.

THE CONCOMITANT USE OF VALPROIC ACID AND CLONAZEPAM MAY PRODUCE ABSENCE STATUS.

There is inconclusive evidence regarding the effect of valproate on serum ethosuximide levels. Patients receiving valproate and ethosuximide, especially along with other anticonvulsants, should be monitored for alterations in serum concentrations of both drugs.

Caution is recommended when DEPAKOTE (divalproex sodium) is administered with drugs affecting coagulation, e.g., aspirin and warfarin. (See "Adverse Reactions" section.)

*Carcinogenesis:* Valproic acid was administered to Sprague-Dawley rats and ICR (HA/ICR) mice at doses of 0, 80 and 170 mg/kg/day for two years. Although a variety of neoplasms were observed in both species, the chief findings were a statistically significant increase in the incidence of subcutaneous fibrosarcomas in high dose male rats receiving valproic acid and a statistically significant dose-related trend for benign pulmonary adenomas in male mice receiving valproic acid. The significance of these findings for man is unknown at present.

*Mutagenesis:* Studies on valproic acid have been performed using bacterial and mammalian systems. These studies have provided no evidence of a mutagenic potential for DEPAKOTE.

*Fertility:* Chronic toxicity studies in juvenile and adult rats and dogs demonstrated reduced spermatogenesis and testicular atrophy at doses greater than 200 mg/kg/day in rats and greater than 90 mg/kg/day in dogs. Segment I fertility studies in rats have shown doses up to 350 mg/kg/day for 60 days to have no effect on fertility. THE EFFECT OF DEPAKOTE (DIVALPROEX SODIUM) ON THE DEVELOPMENT OF THE TESTES AND ON SPERM PRODUCTION AND FERTILITY IN HUMANS IS UNKNOWN.

*Pregnancy:* Pregnancy Category D. See "Warnings" section.

*Nursing Mothers:* Valproate is excreted in breast milk. Concentrations in breast milk have been reported to be 1-10% of serum concentrations. It is not known what effect this would have on a nursing infant. Caution should be exercised when DEPAKOTE is administered to a nursing woman.

**ADVERSE REACTIONS:** Since valproic acid and its derivatives have usually been used with other antiepileptic drugs, it is not possible in most cases, to determine whether the following adverse reactions can be ascribed to valproic acid alone or the combination of drugs.

*Gastrointestinal:* The most commonly reported side effects at the initiation of therapy are nausea, vomiting and indigestion. These effects are usually transient and rarely require discontinuation of therapy. Diarrhea, abdominal cramps and constipation have been reported. Both anorexia with some weight loss and increased appetite with weight gain have also been reported. The administration of enteric-coated divalproex sodium may result in reduction of gastrointestinal side effects in some patients.[2]

*CNS Effects:* Sedative effects have been noted in patients receiving valproic acid alone but are found most often in patients receiving combination therapy. Sedation usually disappears upon reduction of other antiepileptic medication. Tremor has been reported in patients receiving valproate and may be dose related. Ataxia, headache, nystagmus, diplopia, asterixis, "spots before eyes," dysarthria, dizziness, and incoordination have rarely been noted. Rare cases of coma have been noted in patients receiving valproic acid alone or in conjunction with phenobarbital.

*Dermatologic:* Transient increases in hair loss have been observed. Skin rash and erythema multiforme rarely have been noted.

*Psychiatric:* Emotional upset, depression, psychosis, aggression, hyperactivity and behavioral deterioration have been reported.

*Musculoskeletal:* Weakness has been reported.

*Hematologic:* Thrombocytopenia has been reported. Valproic acid inhibits the secondary phase of platelet aggregation. (See "Drug Interactions" section.) This may be reflected in altered bleeding time, Petechiae, bruising, hematoma formation, and frank hemorrhage have been reported. (See "Precautions" section.) Relative lymphocytosis and hypofibrinogenemia have been noted. Leukopenia and eosinophilia have also been reported. Anemia and bone marrow suppression have been reported.

*Hepatic:* Minor elevations of transaminases (e.g., SGOT and SGPT) and LDH are frequent and appear to be dose related. Occasionally laboratory test results include, as well, increases in serum bilirubin and abnormal changes in other liver function tests. These results may reflect potentially serious hepatotoxicity. (See "Warnings" section.)

*Endocrine:* There have been reports of irregular menses and secondary amenorrhea, and rare reports of breast enlargement and galactorrhea occurring in patients receiving valproic acid and its derivatives.

Abnormal thyroid function tests have been reported. (See "Precautions" section.)

*Pancreatic:* There have been reports of acute pancreatitis, including rare fatal cases, occurring in patients receiving valproic acid and its derivatives.

*Metabolic:* Hyperammonemia. (See "Precautions" section.)

Hyperglycinemia has been reported and has been associated with a fatal outcome in a patient with preexistent nonketotic hyperglycinemia.

*Other:* Edema of the extremities has been reported.

**OVERDOSAGE:** Overdosage with valproic acid may result in deep coma.

Since DEPAKOTE tablets are enteric-coated, the benefit of gastric lavage or emesis will vary with the time since ingestion. General supportive measures should be applied with particular attention being given to the maintenance of adequate urinary output.

Naloxone has been reported to reverse the CNS depressant effects of valproate overdosage. Because naloxone could theoretically also reverse the antiepileptic effects of DEPAKOTE, it should be used with caution.

**DOSAGE AND ADMINISTRATION:** DEPAKOTE is administered orally. The recommended initial dose is 15 mg/kg/day, increasing at one week intervals by 5 to 10 mg/kg/day until seizures are controlled or side effects preclude further increases. The maximum recommended dosage is 60 mg/kg/day. If the total daily dose exceeds 250 mg, it should be given in a divided regimen.

*Conversion from DEPAKENE to DEPAKOTE:* In patients previously receiving DEPAKENE (valproic acid) therapy, DEPAKOTE should be initiated at the same total daily dose and dosing schedule.[3] After the patient is stabilized on DEPAKOTE, a twice-a-day or three times-a-day schedule may be instituted in selected patients.

The frequency of adverse effects (particularly elevated liver enzymes) may be dose related. The benefit of improved seizure control which may accompany higher doses should therefore be weighed against the possibility of a greater incidence of adverse reactions.

A good correlation has not been established between daily dose, serum level and therapeutic effect. However, therapeutic valproate serum levels for most patients will range from 50 to 100 mcg/ml. Occasional patients may be controlled with serum levels lower or higher than this range.

As the DEPAKOTE dosage is titrated upward, blood levels of phenobarbital and/or phenytoin may be affected. (See "Precautions" section.)

Patients who experience GI irritation may benefit from administration of the drug with food or by slowly building up the dose from an initial low level.

**HOW SUPPLIED:** DEPAKOTE (divalproex sodium enteric-coated tablets) are supplied as:

| | |
|---|---|
| 125 mg salmon pink colored tablets | |
| Bottles of 100 | (**NDC** 0074-6212-13) |
| 250 mg peach colored tablets | |
| Bottles of 100 | (**NDC** 0074-6214-13) |
| Abbo-Pac® unit dose packages of 100 | (**NDC** 0074-6214-11) |
| 500 mg lavender-colored tablets | |
| Bottles of 100 | (**NDC** 0074-6215-13) |
| Abbo-Pac® unit dose packages of 100 | (**NDC** 0074-6215-11) |

**REFERENCES**
1. Centers for Disease Control, Valproate: A New Cause of Birth Defects — Report from Italy and Follow-up from France, *Morbidity and Mortality Weekly Report* 32(33): 436-439, August 26, 1983.
2. Wilder, B.J., et al, Gastrointestinal Tolerance of Divalproex Sodium, *Neurology* 33: 808-811, June, 1983.
3. Wilder, B.J., et al, Twice Daily Dosing of Valproate with Divalproex, *Clin Pharmacol Ther* 34(4): 501-504, 1983.

Revised: Jan., 1986

**Abbott Health Care Products, Inc.**
**North Chicago, IL 60064**

7033813

# "I gave up private practice ... but I didn't give up practicing."

What a difference... enjoy practicing medicine and let FHP take care of the business end. No worrying about administrative hassles, staffing problems, costly insurance... instead, with scheduled work hours, you're free to enjoy the Southern California lifestyle. Plus, as an FHP physician, you'll receive generous paid vacation, complete malpractice coverage, an excellent retirement plan and many other benefits including, of course, an outstanding salary with tax-deferred compensation plan.

FHP is a well-established and progressive HMO and we enjoy proximity to and support of several university programs in the area. Our steady growth coupled with the opening of our own 125-bed hospital last year, has created career opportunities for BC/BE Primary Care Physicians. For more information about joining our progressive team of professionals, please write or call (800) 446-2255, or (800) 336-2255 within California.

FHP

**Professional Staffing, Dept. 45**
**9900 Talbert Avenue**
**Fountain Valley, CA 92708**


*(Continued from Page 647)*

## PHYSICIANS WANTED

**INTERNIST**—The community of Artesia, New Mexico is seeking an Internist to establish a solo practice. Cross-coverage available from local Internist. Community based financial assistance may be available for the right individual. Family-oriented community with year 'round recreation. Excellent weather. Fully equipped 38-bed new hospital. Submit CV to: Rita Longino, Southwest Community Health Services, PO Box 26666, Albuquerque, NM 87125-6666.

**INTERNIST:** Excellent opportunity for BE/BC Internist(s). Ground floor of integrated health system in desert community, 35 minutes from Palm Springs. Onsite hospital ancillary support, well established tertiary care facilities nearby. Excellent salary, benefits. Send CV to: Tom Schmidt, Professional Health Technologies, 915 Camino Del Mar, Del Mar, CA 92014.

**HEMATOLOGIST-ONCOLOGIST**—To join established multiethnic urban northern California private practice by August 1987. Second language of Mandarin, Cantonese, or Spanish necessary. Send CV and references. Please reply to Number 26, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

**OPHTHALMOLOGIST.** Private practice opportunity available in the community of Clovis, New Mexico. Financial assistance available for the right individual. Please submit CV to: Bill Norris, Southwest Community Health Services, PO Box 26666, Albuquerque, NM 87125-6666; or, call 1 (800) 545-4030, Ext. 8300 for further information.

**PRACTICE FAMILY MEDICINE** with the people in rural Iowa communities where the quality of life is superb. Solo and group practice opportunities available including guaranteed salaries and full benefit packages. For an immediate response please call 1 (800) 247-3121, ext. 8204 (USA).

## PHYSICIANS WANTED

**DERMATOLOGIST.** The community of Clovis, New Mexico is seeking a Dermatologist to establish a private practice. Financial assistance is available. For further information, please submit CV to: Bill Norris, Southwest Community Health Services, PO Box 26666, Albuquerque, NM 87125-6666.

**PEDIATRICIAN WANTED.** On Puget Sound 30 physician multispecialty clinic looking for BE/BC Pediatrician for established practice in our Pediatric Department. Community of 160,000 on beautiful Puget Sound just one hour from Seattle. Excellent salary plus bonus and fringes with early partnership. Contact or send CV to Administrator, The Doctors Clinic, 2512 Wheaton Way, Bremerton, WA 98310; (206) 478-6286.

**RADIOLOGIST,** semi-retired needed part-time to read office x-rays for large musculo-skeletal group in northern California. Interested physicians contact Number 25, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

**OREGON—BC/BE FAMILY PRACTICE** position with long-standing 21 physician multispecialty group practice. Salaried position, regular hours, no call. Office-based walk-in/urgent care setting. Flexible situation; OK for younger or older individual. Beautiful area, equidistant to Portland or San Francisco, dry climate, excellent local cultural amenities. Contact Philip W. Armstrong, Administrator, or Michael F. Bonazzola, MD, at the Medford Clinic, P.C., (503) 773-6271.

**ENT PHYSICIAN**—Outstanding practice opportunity available for full-time, Board certified Otorhinolaryngologist. Fully equipped and furnished office located in prime medical office building with established referral network. Office space and marketing support provided for selected physician eager to quickly build an active practice. Mail CV and letter of professional goals to: "Medical Staff Specialist," 1906-D S.W. 318th Pl., Federal Way, WA 98023.

## PHYSICIANS WANTED

**CALIFORNIA, SAN FRANCISCO BAY AREA**—A leading HMO near San Francisco, California is seeking Board prepared/certified Physicians to staff a busy, urban, full-service Emergency Department. Kaiser Permanente is a large, pre-paid Health Maintenance Organization offering a competitive salary, job security, shareholder status, and generous benefits including health care, life insurance, disability insurance, sick leave, and educational leave. Please address all inquiries to: Hans P. Odsen, MD, Chief, Emergency Department, Kaiser Permanente Medical Center, 1200 El Camino Real, South San Francisco, CA 94080; (415) 742-2513 or 2514.

**NEPHROLOGIST/INTERNIST.** Opening available in 160+ physician group. Need additional Nephrologist/Internist in a busy and fulfilling HMO practice in the San Francisco bay area. Excellent working conditions. Ample opportunities for house staff teaching, clinical faculty appointment, cooperative group participation. Competitive salary. Superb benefit package. Reply with CV to William Peters, MD, Department of Internal Medicine, The Permanente Medical Group, 260 International Circle, San Jose, CA 95119. An Equal Opportunity/Affirmative Action Employer.

**NEW MEXICO—TAOS AND LAS VEGAS:** Excellent full-time hospital emergency department positions are currently available with Spectrum in Taos and Las Vegas. Moderate to low volume emergency departments. Excellent medical and nursing support. Guaranteed rate of reimbursement, occurrence malpractice insurance coverage, CME allowance, reimbursement of professional dues. For additional information on these opportunities, contact Beth Sheldahl, Spectrum Emergency Care, 6275 Lehman Dr., Suite C202, Colorado Springs, CO 80918; 1 (800) 525-3681; (303) 590-1755.

*(Continued on Page 652)*

(Continued from Page 651)

## PHYSICIANS WANTED

**NEUROLOGY.** Position available with small, growth oriented neuro-musculo-rehabilitation clinic. Association with other Neurologist. Board certified/eligible. Excellent practice opportunity with practice costs paid. Superb living conditions on central California coast. Send CV to: David Graham, Administrator, Central Rehabilitation Clinic, Inc., 607 E. Plaza Dr., Ste. C-1, Santa Maria, CA 93454.

**MEDICAL OFFICER** (Internal Medicine) GS-602-14. Immediate opening in USAF Clinic, McClellan Air Force Base. Salary: $55,255 per annum. Internal Medicine Specialist for the Primary Care Department. Provides full range of internal medicine such as cardiology and outpatient medical care of military personnel, active and retired, and their dependents. (Position is temporary.) Contact Elizabeth Haggard at (916) 643-4243. The Federal Government is an Equal Opportunity Employer.

**DIRECTOR OF THE HEALTH CENTER.** The Student Affairs Division of the California Institute of Technology is seeking an individual to direct the overall operations of the Student Health Center and its outreach programs, as well as provide direct patient care in internal medicine. Will be responsible for insuring a high level of efficiency in the delivery of quality health care services for students. This year round assignment of part-time, 16 hours per week (4 hours per day, 4 days per week) requires MD and approximately five years experience following residency. Management experience is desirable. Must be able to interact effectively with students, staff and faculty. The position will be available approximately September 15, 1987. Please send résumé by June 5, 1987 to Caltech, Supervisor of Employment, Position #168, Pasadena, CA 91125. Caltech is an Affirmative Action/Equal Opportunity Employer. Women and minorities are encouraged to apply.

**SOUTHERN CALIFORNIA**

Enjoy professional challenge and growth with a successful and expanding HMO in Southern California. CIGNA Healthplans of California is seeking Specialists and Primary Care physicians committed to concepts of prevention and health maintenance to join our facilities in Los Angeles and Orange Counties. We offer an excellent compensation and benefits package including profit sharing. For consideration, please forward CV to:

**Director/Physician Recruitment**
**CIGNA Healthplans of California**
**505 N. Brand Blvd., Suite 400-49**
**Glendale, CA 91203**

**INPATIENT TRAINING DIRECTOR—GENERAL INTERNIST OR FAMILY PHYSICIAN**—The UCLA/Santa Monica Hospital Medical Center Family Practice Residency Program is seeking a Board certified General Internist or Family Physician with special interest in clinical teaching of residents. Major responsibilities include extensive inpatient teaching and direction of an internal medicine service. The position also emphasizes patient care and curriculum administration. Research skills are desirable. Please send CV to: Charles Payton, MD, Family Practice Residency Program, 1225 Fifteenth St., Santa Monica, CA 90404.

**OB/GYN, PEDIATRICIAN WANTED,** excellent Texas opportunity to practice in a community close to Houston. Enjoy country living at its best with the convenience of Houston within 40 minutes. New high tech 150 bed hospital with good x-coverage. First year guarantee, etc. Call or send CV to Armando L. Frezza, Medical Support Services, 11509 Quarter Horse Trail, Austin, TX 78750; (512) 331-4164.

**PEDIATRICIAN,** BC/BE for family practice community health center in central California area. Competitive salary with excellent fringe benefits. Malpractice is paid. Bilingual/bicultural desirable. Send CV and inquiries to Sequoia Community Health Foundation, 375 N. Fulton, Suite H, Fresno, CA 93701.

## PHYSICIANS WANTED

**SOUTHWEST:** Thomas-Davis Medical Centers, a multispecialty network in Tucson, Green Valley, and Tempe, Arizona, needs an Internist for its central facility in Tucson. FFS practice and doctor owned HMO. Please write or call: James J. Vitali, Executive Administrator, Thomas-Davis Medical Centers, P.C., PO Box 12650, Tucson, AZ 85732; (602) 322-8300.

**WASHINGTON STATE, SEATTLE AREA:** Multispecialty group of nine physicians seeking OB/GYN and Family Practice physician for rapidly growing low risk practice. Community hospital located approximately 10 blocks from Clinic. Enumclaw is a family oriented community, 50 miles from urban area and 60 minutes from outstanding ski resort. Send CV to Barbara Bellack, Clinic Manager, 3021 Griffin Ave., Enumclaw, WA 98022.

**NEPHROLOGIST.** The University of Washington seeks individual at Assistant Professor level. Must be BC/BE in both Nephrology and Infectious Disease, trained in mechanisms of tissue injury research, have independent research grant support and be capable of providing clinical care and teaching in Internal Medicine, Nephrology and Infectious Diseases. Contact W. Couser, MD, Head, Division of Nephrology RM-11, University of Washington, Seattle, WA 98195. The University of Washington is an Equal Opportunity Employer.

**EMERGENCY MEDICINE RESIDENCY PROGRAM DIRECTOR.** The University of California, Davis, School of Medicine is recruiting for a full-time faculty position to assist in the development of an accredited residency program in Emergency Medicine. The position will be at the Assistant or Associate Professor level. The UCD Emergency Department provides comprehensive emergency service and is a major trauma center in Northern California. The Department is an EMT-II Base Station and Training Center and in addition, provides medical direction for the Hospital's Helicopter Program. Candidates must be Board certified or eligible in Emergency Medicine, and be eligible for licensure in California. A letter outlining teaching background, interests, experience, and research in addition to a curriculum vitae and the names of five references must be received by June 30, 1987. Please reply to Robert W. Derlet, MD, Chair of Emergency Medicine Search Committee, Tr. 1219, University of California, Davis, Medical Center, 2315 Stockton Blvd., Sacramento, CA 95817. The University of California is an Affirmative Action/Equal Opportunity Employer.

**CALIFORNIA, SAN FRANCISCO:** Excellent opportunity for well qualified full-time Emergency Physician. Board eligible/certified EM, IM, Surg, FP. Exceptional salary and benefits package. Send letter of interest and CV to: Daniel Matulich, MD, Director, Emergency Services, French Hospital, 4131 Geary Blvd., San Francisco, CA 94118.

**PEDIATRICIAN BC/BE** for hospital-based teaching practice. Interest and training in neonatology and critical care pediatrics preferred. Join two full-time pediatricians and two full-time neonatologists in hospital with Level II ICN and busy inpatient and outpatient services. Paid malpractice. Salary negotiable based on training and experience. Submit CV and references to: Patricia A. Dixon, MD, Director/Neonatal Services, San Joaquin General Hospital, PO Box 1020, Stockton, CA 95201; (209) 468-6600. AA/EOE.

**CHIEF OF PEDIATRICS.** Natividad Medical Center, a University of California, San Francisco affiliated hospital, located in beautiful Monterey County, is seeking a Board certified/Board eligible Pediatrician. Preference given to physician with Chief Residency or sub-specialty experience. Natividad sponsors a family practice residency program with 18 residents. Salary range from $73,000 to $78,000 depending upon qualifications with excellent benefit package. Natividad Medical Center is an Affirmative Action Equal Opportunity Employer. For further information, please mail CV or contact: Richard McClurkin, Personnel Officer/Search Board Leader, PO Box 8-1611, Salinas, CA 93912-1611; (408) 757-0581.

## PHYSICIANS WANTED

**INTERNIST**—We are seeking a BC or BE General Internist to join our hospital and clinic-based group of 13 in providing primary patient care with active participation in a university affiliated teaching program. We invite all applicants but desire an enthusiastic clinician role model with excellent communication skills interested in patient care and teaching. Competitive salary and excellent fringe benefits. Send CV to Kent Imai, MD, Department of Medicine, Santa Clara Valley Medical Center, 751 S. Bascom Ave., San Jose, CA 95128.

**FAMILY PRACTITIONER.** Full-time BE/BC FP for growing multispecialty group in sunny California. Some Spanish helpful. First year compensation, benefits, and malpractice. Partnership potential second year. Send CV to Number 29, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

**MEDICAL DIRECTOR, STATE OF WASHINGTON, DEPARTMENT OF LABOR AND INDUSTRIES.** The Washington State Fund solicits applications from qualified individuals for the position of Medical Director. The State Fund insures 115,000 employers and 1.3 million workers for industrial injuries and diseases. 150,000 claims are accepted annually. Duties of the Medical Director include policy development, assuring injured workers receive good quality medical care, conducting research on optimal treatment methods for occupational injuries and diseases and supervising physicians and nurses supporting claims adjudication. A faculty appointment in the Department of Environmental Health, School of Public Health and Community Medicine, University of Washington, is available at the level of assistant, associate or full research professor, depending upon experience and qualifications. The candidate will be expected to develop research programs independently or in collaboration with other faculty and to contribute to teaching programs in occupational health. For further information contact Rebecca Zeppa, Health Services Analysis, HC-251, Department of Labor and Industries, Olympia, WA 95804-0631; (206) 586-0768. The State and University of Washington are Equal Opportunity/Affirmative Action Employers. This position closes June 1, 1987.

**INTERNIST OR SURGEON,** Board certified/eligible, needed immediately for rural community in beautiful N.E. Washington for family practice referral-based service area of approximately 15,000. Inquiries or résumés to: Administrator, Newport Community Hospital, PO Box 669, Newport, WA 99156.

**ORTHOPEDIC SURGEON.** Full-time Orthopedic Surgeon to join growing multispecialty group in sunny California. Salary, incentive, malpractice and benefits. Great potential for right physician. Individual ownership. Send CV to Number 30, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

**EXCELLENT TEXAS OPPORTUNITY,** for a F/P, G/P, G/S, and I/M person, to develop a practice in a lake area community, in the beautiful Piney Woods area of east Texas. The rewards for your efforts will be great. Send CV to, Medical Support Services, 11509 Quarterhorse Trail, Austin, TX 78750 or call Armando L. Frezza, (512) 331-4164.

**INTERNIST**—Growing Long Beach, California industrial clinic seeks Internist to evaluate and treat Workers' Compensation patients. Position requires good communication skills and good patient rapport. No nights or weekends. Excellent benefits. Contact R. Unitan, 4237 Atlantic Ave., Long Beach, CA 90807; (213) 424-0423.

**INTERNAL MEDICINE.** Full-time BE/BC active Internist for multispecialty group in sunny California. Office/hospital and consult practice. Spanish a plus. Salary, benefits, and malpractice. Potential for partnership second year. Send CV to Number 31, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

(Continued on Page 654)

# THE ARIZONA MEDICAL ASSOCIATION, INC.

## 1987 ANNUAL MEETING

## June 4 - 6, 1987, Phoenix Arizona

### The Pointe at South Mountain • 7777 South Pointe Parkway

| | | | |
|---|---|---|---|
| **THURSDAY, JUNE 4, 1987** | 8 a.m. - 12 noon | **Current Perspectives Program** | |
| | | Surgery | Coronado |
| | | Internal Medicine | Cortez |
| | | Pediatrics | Sonora |
| | | Obstetrics & Gynecology | Kachina |
| | | Family & Community Medicine | Yucca |
| | 9 a.m. - 10:30 a.m. | *Auxiliary Opening Meeting* | Apache |
| | 10:30 a.m. - 11:30 a.m. | *Auxiliary Legislation Workshop* | Apache |
| | 11:30 a.m. - 1 p.m. | *Auxiliary Luncheon* | West Garden |
| | 1 p.m. - 5 p.m. | **Current Perspectives Program** | |
| | | Surgery | Coronado |
| | | Internal Medicine | Cortez |
| | | Emergency Medicine | Sonora |
| | | Dermatology | Kachina |
| | | Orthopedic Surgery & Sports Medicine | Yucca |
| | 1 p.m. - 5 p.m. | Hospital Medical Staff Section | |
| | | Program and Annual Meeting | Zuni |
| | 1 p.m. - 4 p.m. | Arizona Orthopaedic Society | Palo Verde Room #1 |
| | 2 p.m. - 3:30 p.m. | *Auxiliary Reference Committee* | Apache |
| | 2 p.m. - 3:30 p.m. | *Auxiliary Reference Committee* | Grand Canyon 1 |
| | 2 p.m. - 5 p.m. | Arizona Chapter, American | |
| | | College of OB/GYN | Saguaro |
| | 3:30 p.m. - 5 p.m. | *Auxiliary House of Delegates* | Apache |
| | 7 p.m. | Reception | Rustler's Rooste |
| | 8 p.m. | M*A*S*H BASH | Rustler's Rooste |
| **FRIDAY, JUNE 5, 1987** | 6 a.m. - 8 a.m. | Executive Committee Breakfast | #6002 |
| | 7:30 a.m. - 8:30 a.m. | *Auxiliary County Caucus* | Apache |
| | 8 a.m. - 10 a.m. | Board of Directors | Cortez |
| | 8:30 a.m. - 10 a.m. | *Auxiliary House of Delegates* | Apache |
| | 10 a.m. - 12 noon | House of Delegates | Pima |
| | 11 a.m. - 12 noon | *Auxiliary Workshop* | Apache |
| | 12 noon - 4 p.m. | Past Presidents' Luncheon | #6001 |
| | 12 noon - 3 p.m. | *Auxiliary Luncheon* | Cortez |
| | 2 p.m. - 5 p.m. | Amendments Reference Committee | Pima |
| | 2 p.m. - 5 p.m. | Resolutions Reference Committee | Hopi |
| | 3 p.m. - 5 p.m. | *Auxiliary Summer Board Meeting* | Apache |
| | 7 p.m. | President's Reception | West Garden |
| | 8 p.m. | President's Banquet | Cortez/Coronado |
| **SATURDAY, JUNE 6, 1987** | 6:30 a.m. - 8 a.m. | Maricopa County Caucus | Apache |
| | 6:30 a.m. - 8 a.m. | Pima County Caucus | Pima |
| | 8 a.m. - 12 noon | House of Delegates | Zuni |
| | 12 noon - 3 p.m. | Board of Directors' Luncheon | Navajo |
| | 1:30 p.m. - 4:30 p.m. | Young Physicians Section | Hopi |
| | 4:30 p.m. - 5:30 p.m. | Young Physicians Section Reception | Grand Canyon 2 |

FOR ADDITIONAL INFORMATION, please contact: Arizona Medical Association, 810 W. Bethany Home Rd., Phoenix, AZ 85013 • (602) 246-8901

(Continued from Page 652)

## PHYSICIANS WANTED

**ORTHOPEDIC SURGEON.** Natividad Medical Center, a University of California, San Francisco affiliated hospital, located in beautiful Monterey County, is recruiting an Orthopedic Surgeon. This position combines teaching and practice. The hospital sponsors a family practice residency program with 18 residents and has a very active trauma service with a regional paramedic base station. An attractive base salary with fee for service incentive option is negotiable. Natividad Medical Center is an Affirmative Action Equal Opportunity Employer. For further information, please mail CV or contact: Richard McClurkin, Personnel Officer/Search Board Leader, PO Box 8-1611, Salinas, CA 93912-1611; (408) 757-0581.

**NORTHERN CALIFORNIA:** Allergist, ABAI certified/eligible needed to join staff of Kaiser Permanente, Vallejo (near San Francisco). Full-time position available approximately July 1, 1987. Large HMO with excellent benefits. Contact or send CV (707) 648-6282, R. Sachs, MD, Dept. of Allergy, Kaiser Permanente, 975 Sereno Dr., Vallejo, CA 94589.

**OB/GYN,** BC/BE for family practice community health center in central California area. Competitive salary with excellent fringe benefits. Malpractice is paid. Bilingual/bicultural desirable. Send CV and inquiries to Sequoia Community Health Foundation, 375 N. Fulton, Suite H, Fresno, CA 93701.

**RESEARCH ASSISTANT** in medicine/nephrology lab: Design method for separation of different-molecular-weight fraction of a polymer of dextran in biological samples to evaluate pore radius of glomerular basement membrane by dextran model in renal study. Analyze research data through clinfo system. Participate in selected research and methods development projects for renal function studies. Require MS in Analytical Chemistry, specialize in size exclusion chromatography with at least two years experience in chromatography field. Through job-related experience, demonstrate ability to: 1. develop procedures for biological sample purification, 2. design, set-up the proper size-exclusion HPLC instruments, 3. maintain/troubleshoot the analytical system independently, 4. develop the new analytical methods, 5. instruct computer programmer to develop program for computing integrator, 6. analyze/interpret results by doing statistical evaluation through clinfo system. $2,098 per month. Job location: Palo Alto, California. Send résumé to: Number 28, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602; no later than June 5, 1987.

**PHYSIATRIST—BC/BE** for northern California practice oriented towards clinical, occupational and evaluative medicine; qualified applicants will have EMG/NCS, EEG experience, be familiar with med-legal environment and seek a growth oriented opportunity; send current CV, letter of interest and compensation requirements to: Box 164, 1550 California St., Suite 6, San Francisco, CA 94109.

**OREGON:** Emergency department Medical Director and full-time Staff Physician are needed at client hospital located in community on the Columbia River in north central Oregon. Full service community hospital with moderate volume emergency department. Guaranteed rate of reimbursement, occurrence malpractice insurance coverage, CME allowance, reimbursement of professional dues, plus directors receive paid health benefits which include dependents. For additional information on this opportunity, contact Bill Salmo, Spectrum Emergency Care, 6275 Lehman Dr., Suite C202, Colorado Springs, CO 80918; 1 (800) 525-3681; (303) 590-1755.

**INTERNIST NEEDED FULL-TIME.** Primary Care position for Board certified Internist is now available with a growing San Francisco Health Plan. The position includes both inpatient and outpatient responsibilities. Send CV to: Medical Director, French Health Plan, 4131 Geary Blvd., San Francisco, CA 94118.

## PHYSICIANS WANTED

**POSITION AVAILABLE NOW** for Board eligible or Board certified OB/GYN Physician in the Department of OB/GYN, Stockton Medical Offices, The Permanente Medical Group, Inc., a multispecialty HMO group providing medical care services for Kaiser Foundation Health Plan. Ideally located in northern California within two hours of San Francisco, the Sierra Mountains, and Monterey/Carmel. Excellent benefits include paid malpractice, life insurance, retirement programs, medical and dental care, vacation and educational leave. Competitive salary. Send curriculum vitae to Physician Recruitment, The Permanente Medical Group, Inc., 1305 Tommydon St., Stockton, CA 95210. An Equal Opportunity Employer.

**MD NEEDS**—OB/GYN and IM or IM/Oncologist needed for a multispecialty group practice in Helena, Montana. Capital of state, population 30,000-35,000, small private college, close to Rocky Mountains with fishing, hunting and outdoor sports. Midway between Glacier and Yellowstone Parks. Reply to Dan B. Smelko, Helena Medical Clinic, P.C. 1930 9th Ave., Helena, MT 59601.

**FAMILY PRACTITIONER** to join established, growing multispecialty group in Marin County. Board certified/eligible required. This group of 58 + physicians provides care to both fee-for-service and prepaid patients. Excellent practice opportunity and superb living conditions. Guaranteed starting salary with ownership potential. Send CV to: RVMC, Inc., 1350 S. Eliseo Dr., Greenbrae, CA 94904, ATTN: Personnel.

**OB/GYN**—wanted to join rapidly growing group practice affiliated with large medical center in Seattle, Washington. Call Yolanda Randlett, Manager, (206) 328-2112.

**INTERNAL MEDICINE**—Full-time position for a Board certified or Board eligible Internist in a 15-resident, 7-faculty rural family medicine program affiliated with the University of California, Davis. Duties include supervision of residents on the medical ward and in the ICU/CCU areas. Excellent salary. Send inquiries with CV to E. Hughell, MD, Director, Family Practice Residency Program, Merced Community Medical Center, PO Box 231, Merced, CA 95341; (916) 385-7172. EOE.

**INTERNIST**

Urgently needed in Sun Valley/Ketchum, Idaho multispecialty small group practice. Will assume large practice. Excellent climate, unlimited recreational facilities, and very good schools. Income guarantees available. Bryan Stone, MD, or Byron McCurdy, Administrator, PO Box 2198, Ketchum, ID 83340; (208) 726-9361.

**SALT LAKE AREA**—General Practitioner needed for new, fully equipped facility. Excellent salary—benefit package, plus percentage. Enjoy outdoor recreation, skiing, hunting, fishing, as well as cosmopolitan living. Reply to Number 34, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

**MULTISPECIALTY GROUP** in San Francisco bay area looking for Board certified Family Practitioner for beautiful satellite office. Competitive salary and later incentive program. Contact: David Louis, MD, 3100 Telegraph Ave., Oakland, CA 94609; (415) 273-8150.

**WE HAVE FULL AND PART-TIME LOCUM TENENS** opportunities available with guaranteed incomes and paid malpractice. For more information, contact John Smith, Locum Tenens, Inc. (A Division of Jackson and Coker), 400 Perimeter Center Terrace, Suite 760 WJM, Atlanta, GA 30346; Tel. 1 (800) 544-1987.

## SITUATION WANTED

**BOARD CERTIFIED OBSTETRICIAN-GYNECOLOGIST,** 46, seeking position in northern New Mexico, Albuquerque area. Prefer group practice. Please reply to Number 27, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

## SITUATION WANTED

**PLASTIC SURGEON** completed residency and postgraduate training August 1986. Interviewing now. Prefer California, Utah, Oregon, Washington, Arizona. Please reply Number 21, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

**INTERNIST,** Board certified in Internal Medicine, desires full-time employment with group or HMO. Physician also has subspecialty of Oncology and Hematology. Will practice primary care internal medicine and/or oncology and hematology. Also interested in position of medical or hospital administrator. Physician has private practice and HMO experience. Site must be within 45 minutes or 25 miles of Long Beach, California. Available May 1987. Please call Dr David Dworkin, at (213) 494-7473 or (714) 722-6926 or write to 6250 Majorca Circle, Long Beach, CA 90803.

**PULMONARY DISEASE AND INTERNAL MEDICINE—**Experienced Pulmonologist seeking a change in practice location. Board certified in Internal Medicine and Pulmonary Disease. Experienced in invasive procedures. Wish to join a group practice. Prefer northern California. Reply to Number 32, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

## LOCUM TENENS

**LOCUM TENENS, INC.** (A Division of Jackson and Coker), can staff your practice from 2 weeks to 52 weeks, malpractice insurance for all 50 states, contact John Smith, 400 Perimeter Center Terrace, Suite 760 WJM, Atlanta, GA 30346; Tel. 1 (800) 544-1987.

**LOCUM TENENS SERVICE**
**WESTERN PHYSICIANS REGISTRY**

*. . . offers coverage for vacation or continuing education. To arrange coverage for your practice or to participate as temporary physician, contact:* **Carol Sweig, Director, 1315 Evans Avenue, San Francisco, CA 94124; (415) 826-7676.**

## OFFICE SPACE

**GROWTH AREA OF SANTA CLARA VALLEY.** New medical office space for lease in the growth area of Silicon Valley . . . Morgan Hill, California. Easy hospital access, abundant parking, well located, generous tenant improvement allowances. Excellent referral sources for Family Practitioner, Pediatrician, and OB/GYN already in this newly available complex. Contact Dr Jon Hatakeyama, (408) 779-7391.

**GLENDALE, ARIZONA.** Medical office space available. 705 square feet at the Thunderbird Medical Plaza I, 5422 W. Thunderbird Rd., Ste. 19C, Glendale, AZ. Call Sharad Bellapravalu, MD, (602) 938-1300.

## EDICAL EQUIPMENT

**COMPLETE SET-UPS TO SINGLE ITEMS**
Save on your medical equipment needs by buying quality used instead of new! Burdick EK-8 like new 1150, Coulter S + cell counter, Ames Seralyzers #5110A— $500, Ames Seralyzers #5181 (like new) $1,500, Neurology equipment-Grass 17 chan EEG, Grass 4 chan. Evoke Potential, Teca TE-4 with computer all for $21,500. Alpha Bio-Feedback Chamber (like new), Toshiba 300 mas Portable X-Ray self-propelled $4,000. Grass EEG machine, 8 channel $3,500, Cambridge Stress System $5,200, Autospiro Spirometer $3,200, Coulter M430 cell counter with printer $7,900. This is a partial, call or write for complete listing.
**MEDEXCHANGE (214) 369-3960**
**PO Box 18164, Dallas, TX 75218.**

(Continued on Page 656)

# WYOMING MEDICAL SOCIETY

84th ANNUAL MEETING WMS HOUSE OF DELEGATES AND SCIENTIFIC SESSION

JUNE 25-28, 1987 • JACKSON LAKE LODGE, MORAN, WYOMING • GRAND TETON NATIONAL PARK

## WMS ANNUAL MEETING AND SCIENTIFIC SESSION

### THE LABORATORY'S CONTRIBUTION TO CLINICAL MEDICINE

### THURSDAY, JUNE 25, 1987

8:00 AM REGISTRATION/EXHIBITS

8:30 AM WMS HOUSE OF DELEGATES OPENING SESSION

10:30 AM REFERENCE COMMITTEES

1:15 PM LEE K. HERMANN, MD
WMS President
*Welcoming Remarks*

1:30 PM CARL E. SPEICHER, MD
*The Laboratory and the Healthy Patient: What Do We Really Need?*

2:15 PM CARL E. SPEICHER, MD
*The Outpatient: A Look at the More Common Diagnostic Problems, New Aspects of Laboratory Testing*

3:00 PM Coffee Break

3:15 PM JOHN C. NEFF, MD
*Infectious Mononucleosis: The Child, the Adolescent and the Adult—Current Concepts*

4:00 PM QUESTION AND ANSWER ROUNDTABLE

4:30 PM RECESS SCIENTIFIC SESSION

6:00 PM WELCOME TO THE TETONS SOCIAL HOUR
(Hosted by The Doctors' Company)

### FRIDAY, JUNE 26, 1987

8:00 AM REGISTRATION/EXHIBITS

9:00 AM LEE K. HERMANN, MD
*Introductory Remarks*

9:00 AM ARTHUR E. PELLEGRINI, MD
*What Is That Funny Looking Pigmented Skin Lesion?*

9:45 AM ARTHUR E. PELLEGRINI, MD
*Current Therapeutic Approaches to the Aggressive Melanocytic Tumors*

10:30 AM Coffee Break

10:45 AM CARL E. SPEICHER, MD
*Problem Cases Within the Hospital: The Contribution of the Laboratory*

11:30 AM QUESTION AND ANSWER ROUNDTABLE

11:45 AM Lunch Break

2:00 PM THE DOCTORS' COMPANY RISK MANAGEMENT TEAM
*A Mock Trial*

4:00 PM Recess Scientific Session

6:00 PM WMS PRESIDENT'S RECEPTION AND BANQUET
MICHAEL J. SULLIVAN
Governor of Wyoming, *Speaker*
*Entertainment and Dancing*

### SATURDAY, JUNE 27, 1987

8:00 AM REGISTRATION/EXHIBITS

9:00 AM LEE K. HERMANN, MD
*Introductory Remarks*

9:00 AM JOHN C. NEFF, MD
*Hepatitis: Current Applications of the Serologic Markers*

9:45 AM JAMES M. AVENT, MD
*The Thin Needle: Uses and Abuses*

10:30 AM Coffee Break

10:45 AM JOHN C. NEFF, MD
*Let's Look at the Complications of Blood Transfusions*

11:30 AM QUESTION AND ANSWER ROUNDTABLE

12 NOON Recess Scientific Session
*Afternoon Free*

6:00 PM SOCIAL HOUR
(Hosted by Capitol Recoveries)

### SUNDAY, JUNE 28, 1987

9:00 AM WMS HOUSE OF DELEGATES CLOSING SESSION

### FACULTY

**James M. Avent, MD**
Assistant Professor
University of Utah
Cytopathologist
St. Mark's Hospital
Salt Lake City

**John C. Neff, MD**
Professor of Pathology
Ohio State University
Columbus, Ohio

**Arthur Pellegrini, MD**
Captain, United States Navy
Department of Dermatology
United States Naval Hospital
San Diego

**Carl E. Speicher, MD**
Professor of Pathology
Director of Clinical Labs
Ohio State University
Columbus, Ohio

**Risk Management Team**
The Doctors' Company
Santa Monica, California

WYOMING Medical Society

WYOMING MEDICAL SOCIETY
P.O. Box 4009
Cheyenne, WY 82003-4009
Phone (307) 635-2424

### REGISTRATION FORM FOR PHYSICIANS ATTENDING THE WMS ANNUAL MEETING

JUNE 25-28,1987 • JACKSON LAKE LODGE • MORAN, WYOMING

NAME _____ SPOUSE'S NAME _____

ADDRESS _____ ZIP _____

____ Registration Fee ($80 for members $100 for nonmembers) . . . . . $_____

____ Banquet tickets @ $25 per person . . . . . $_____

____ Auxiliary Luncheon tickets @ $10 per person . . . . . $_____

TOTAL $_____

Checks made payable to the Wyoming Medical Society must accompany this form and be sent to:

WYOMING MEDICAL SOCIETY
P.O. DRAWER 4009
CHEYENNE, WY 82003

____ Send Jackson Lake Lodge reservation form and Grand Teton Park lodging information.

# What Every Physician's Spouse Should Know

**A series of booklets on topics of special interest to medical families published by the American Medical Association Auxiliary**

**Professional Liability**
■ Scope of problem ■ Legal process ■ Coping

**Impairment**
■ Causes ■ Impact on family ■ Getting help

**Survival Tips for Resident Physician/ Medical Student Spouses**
■ Marriage in the training years ■ Stress ■ Finances

**Marriage**
■ Who players are ■ Special concerns ■ Stages of medical career

**Retirement and Estate Planning**
■ Making retirement years fulfilling ■ Providing for the family's future

**MAIL ORDER FORM TO:**
**American Medical Association Auxiliary, Inc.**
**535 N. Dearborn St., Chicago, IL 60610**

Please send me the following publications in the series on ***What Every Physician's Spouse Should Know:***

# of copies
___ Impairment
___ Professional Liability
___ Survival Tips for Resident Physician/ Medical Student Spouses
___ Marriage
___ Retirement and Estate Planning
**(AVAILABLE FEB. 1, 1987)**

Each booklet is $3 per copy for AMA Auxiliary members and $5 per copy for non-members.

Enclosed is my check in the amount of $_____ made payable to the AMA Auxiliary Check must accompany order form

NAME _____

ADDRESS _____

CITY/STATE/ZIP _____

TELEPHONE (  ) _____

*(Continued from Page 654)*

## MEDICAL EQUIPMENT

**QUINTON MODEL 16-20 TREADMILL** with 620 programmer defibrillator; Fairchild Audio-visual Patient Education System with tapes; Clay Adams Hematology Analyzer Model HA3; two water baths for 37-56°; Nuclear Lab Isotope counter for digoxin levels and other RIA determinations (IN-V-TRON Model 2000 for I-121-125, TC-99). Call (206) 752-5563.

**50% OFF** previously owned medical, laboratory, office, x-ray, ultra-sound equipment in excellent condition. We buy, sell, broker and repair. Office appraisals by Certified Surgical Consultants. Call Medical Equipment Resale, Inc., 24026 Haggerty Rd., Farmington Hills, MI 48018; (313) 477-6880 anytime.

## PRACTICES AVAILABLE

**OB/GYN PRACTICE FOR SALE IN HOBBS, NEW MEXICO.** Gross $320,000-$360,000. OB/GYN coverage available. 50-80 continuing OB's to be delivered by prospective buyer. Must act quickly—offer not available after May 31, 1987. (505) 392-1512, (505) 392-2343.

**CALIFORNIA, MONTEREY BAY AREA PEDIATRIC PRACTICE** for sale. Share call with three Board certified Pediatricians. Walk to hospital with level II Nursery. Office equipment and furnishings included. Established 11 years, retiring for health reasons. Call (408) 728-4223 evenings.

**FAMILY PRACTICE-GENERAL SURGERY.** Multiple practice situation, long established. Prime Orange County, California beach city location. Adjacent to modern hospital with ICU/CCU. Includes equipment, assumable lease. Reply to Number 17, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

**FOR SALE ESTABLISHED NEUROLOGY PRACTICE,** 40 miles south of Seattle next to major adult and ped. hospital. CT, MRI available; share call. EEG, EMG, evoked potentials in office. Gross $280K, sell $60K plus acct. rec. (if desired), financing available. Available 1987, retire for health reasons and available during transition. Call (206) 572-8663, leave name and phone. Will return call after hours.

**ACTIVE ADULT AND PEDIATRIC ALLERGY PRACTICE** for sale in Albuquerque, New Mexico. Available immediately. Pleasant climate—good gross—excellent hours—and negotiable terms. Reply Number 33, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

**OTORHINOLARYNGOLOGY—SOUTHERN CALIFORNIA**—Established 14 years. Retiring Doctor. 80% patient referral. Outlying area. Collected $300K in 1986. High Net. Traditional practice with additional business available. Many other opportunities available. Professional Practice Sales (714) 832-0230.

**PRACTICE FOR SALE IN WESTERN MONTANA.** Three-physician Family Practice Clinic. Well established large practice of 30 years with excellent reputation. Computerized office. Well-equipped lab and x-ray departments. Diagnostic equipment including flexible 63 centimeter sigmoidoscope, three channel ECG, computerized stress test equipment, pulmonary function equipment and more. Twelve exam rooms, two minor surgery rooms, three Doctor's personal offices. Offices located in a 16,000 square foot office building renting also to dentists and other professionals. Office building can be purchased if desired. University community of 27,000 population, trade area of 80,000. New community hospital. Opportunity for two physicians to come into the practice immediately. Send CV. Inquire for income/expense details of practice. Write to B. John Heetderks, Jr., MD, 20 E. Olive, Bozeman, MT 59715.

**PHOENIX FAMILY PRACTICE**—Solo adult practice, excellent location, collections over $250,000. Write or call Mr Rinde, PO Box 444436, Phoenix, AZ 86064; (602) 224-0349.

## PRACTICES AVAILABLE

**RETIRING BECAUSE OF ILLNESS**—Office available immediately. Equipment available. Rent/lease. Active general surgery practice. Good location also for OB/GYN, ORTHO. Southern California 60 miles east of Los Angeles. Charles Engel, MD, 128 East G St., Colton, CA 92324; (714) 825-6411.

**INTERNAL MEDICINE PRACTICE FOR SALE:** Aptos, California "On the Monterey Bay." 39 year established, responsible private practice. Three excellent hospitals within 10 mile radius. All specialties available. Limited to Board eligible or certified Internists. Contact: Administrator, PO Box 325, Aptos, CA 95001; (408) 688-3071.

## PRACTICE OPPORTUNITIES

**CALIFORNIA:** Derm, IM, Ophthal, OB/GYN, Otolaryngology, Neurosurgery, Occupational Medicine, Family, Surg, Allergy, Ortho, Psych, Pulm, Radiology, Rheum, Ped plus many others. Mary Bradshaw, Practice Broker/Recruiter, Valuations, 21 Altamount Dr., Orinda, CA 94563; (415) 376-0762.

## COMPUTER INFORMATION

**COMPUTERIZE YOUR MEDICAL BILLING.** Remarkably easy-to-use software. Prints bills, statements, insurance forms. Menu-driven. Reports aging balances, referral sources, income by time period, medical procedure codes and more. Installs automatically. IBM and compatibles—hard disk or floppies. Solo practice only $399. Group practice only $499 (Calif. add tax) MC/Visa. Full customer support. Demo disk w/46 pg manual ($10 + $3s/h). Call or write REM Systems, Inc., 180 Emerson St., Palo Alto, CA 94301; (415) 322-0369.

## SEMINARS

**MALPRACTICE AND PRACTICE MANAGEMENT TAX DEDUCTIBLE SEMINARS** held weekly in San Francisco, Lake Tahoe, San Diego, and Anaheim. Call California Seminars at 1 (800) 325-7934. In California call 1 (800) 526-6699.

## MISCELLANEOUS

**EXECUTIVE QUALITY RETREAT:** overlooking Flathead Lake and Montana mountains. Anxious to sell. Located near cultural/recreational area. Easy access to local activities and international airport. Call (406) 837-5851 or write PO Box 250, Bigfork, MT 59911.

***MEDICAL SPANISH — EASY!***
Speak to patients in everyday Spanish.
*Complete 6-cassette course with manual/dictionary, pocket guide. All basic terms and procedures. $95 plus tax.
RESULTS GUARANTEED OR MONEY REFUNDED!
**CALL/WRITE FOR FACTS ON OTHER MATERIALS, FREE MEDICAL SPANISH NEWSLETTER!**
CSLA
**CALIFORNIA SPANISH LANGUAGE ASSOC.**
**P.O. Box 3522-J, San Diego, CA 92073-0590**
**(619) 544-0548**

*Ads Get Results!*

CLASSIFIED INFORMATION
**(415) 863-5522 EXTENSION 244**

## WESTERN STATE MEDICAL ASSOCIATIONS' MEETINGS

**Alaska State Medical Association**—2401 E 42nd Ave, Suite 104, Anchorage 99508. (907) 562-2662. Annual Meeting: June 3-7, 1987, Juneau.

**Arizona Medical Association, Inc**—810 W Bethany Home Rd, Phoenix 85013. (602) 246-8901. Annual Meeting: June 4-6, 1987, Pointe South Mountain, Phoenix.

**California Medical Association**—PO Box 7690, San Francisco 94120-7690. (415) 863-5522. Annual Meeting: March 4-9, 1988, Bally's Grand Hotel, Reno.

**Colorado Medical Society**—PO Box 17550, Denver 80217-0550. (303) 779-5455. Annual Meeting: September 9-12, 1987, Beaver Run, Breckenridge.

**Hawaii Medical Association**—320 Ward Ave, Suite 200, Honolulu 96814. (808) 536-7702. Annual Meeting: October 10-12, 1987, Kauai Surf, Kauai.

**Idaho Medical Association**—305 W Jefferson, PO Box 2668, Boise 83701. (208) 344-7888. Annual Meeting: July 27-August 2, 1987, Coeur d'Alene.

**Montana Medical Association**—2012 11th Ave, Suite 12, Helena 59601. (406) 443-4000. Annual Meeting: October 1-3, 1987, Copper King Inn, Butte.

**Nevada State Medical Association**—3660 Baker Lane, Reno 89502. (702) 825-6788. Annual Meeting: 1988, date and place to be announced.

**New Mexico Medical Society**—303 San Mateo NE, Suite 204, Albuquerque 87108. (505) 266-7868. Annual Meeting: May 6-8, 1987, Clarion Four Seasons, Albuquerque.

**Oregon Medical Association**—5210 SW Corbett Ave, Portland 97201. (503) 226-1555. Annual Meeting: (House of Delegates only): 1988, date and place to be announced.

**Utah State Medical Association**—540 E Fifth South, Salt Lake City 84102. (801) 355-5290. Annual Meeting: September 9-11, 1987, Marriott Hotel, Salt Lake City.

**Washington State Medical Association**—900 United Airlines Bldg, 2033 6th Ave, Seattle 98121. (206) 441-WSMA. Annual Meeting: September 17-20, 1987, Sheraton, Tacoma.

**Wyoming Medical Society**—PO Drawer 4009, Cheyenne 82003-4009. (307) 635-2424. Annual Meeting: June 25-29, 1987, Jackson Lake Lodge, Moran.

## ADVERTISING INDEX


ABBOTT LABORATORIES
*Depakote* ..... 649, 650
AMERICAN MEDICAL ASSOCIATION ..... 656
ARIZONA MEDICAL ASSOCIATION ..... 653
ASSOCIATION OF SLEEP DISORDER CENTERS ... 552
AUDIO DIGEST ..... 541
CAMPBELL LABORATORIES
*Herpecin-L* ..... 545
CLASSIFIED ADVERTISING .... 647, 651, 652, 654, 656
COOPERATIVE OF AMERICAN PHYSICIANS ..... 538
CURTIS INFORMATION SYSTEMS ..... 551
DLC DIAGNOSTICS ..... 658
ELI LILLY & COMPANY
*Keflet* ..... 542
FAMILY PRACTICE RECERTIFICATION ..... 545
FHP PROFESSIONALS ..... 651
GEIGY PHARMACEUTICALS
*Lopressor* ..... 543, 544
HOFFMANN-LA ROCHE LABORATORIES
*Dalmane* ..... 2nd cover, 535, 536
*Rocephin* ..... 3rd and 4th covers
IDAHO MEDICAL ASSOCIATION ..... 643, 644, 645
MARION LABORATORIES
*Cardizem* ..... 553, 554
McNEIL LABORATORIES
*Tylenol* ..... 537
MEDICAL OFFICE CONSULTANTS ..... 569
MONTANA STATE UNIVERSITY ..... 568
PRINCETON PHARMACEUTICAL PRODUCTS
*Corgard* ..... 548, 549
A. H. ROBINS COMPANY
*Micro-K* ..... 546
SIERRA MEDICAL ..... 641
SMITHKLINE BECKMAN
*Dyazide* ..... 570
SOUTHERN CALIFORNIA PHYSICIANS INSURANCE EXCHANGE ..... 559
SYSTEMS PLUS INC. ..... 561
SYZYGY COMPUTER SYSTEMS, INC. ..... 565
UNIVERSITY MICROFILM ..... 536
UPJOHN COMPANY
*Medrol* ..... 555
*Motrin* ..... 566, 567, 568
*Xanax* ..... 556, 557, 558
THE WESTERN JOURNAL OF MEDICINE
*Subscription Information* ..... 558
WILLIAMS, WRIGHT & ASSOCIATES, INC. ..... 539
WYOMING MEDICAL SOCIETY ..... 655

# DLC Diagnostics Offers
## Blood Chemistry and Hematology Testing
## in your own office *NOW!*

DLC provides complete
installation and training.

### CELL–DYN HEMATOLOGY ANALYZERS

**The ultimate in low cost hematology testing.**
**An invitation to join thousands of satisfied customers.**

We offer a complete line of economical CELL-DYN hematology instruments designed to fill any cell counter need. CELL-DYN analyzers use one-touch discrete testing and incorporate user-friendly programming. Choosing CELL-DYN insures reliability. A recent survey of over 1500 CELL-DYN instruments (picked randomly) indicated an amazing 312 days between customer-requested service calls. Now that's reliability you can depend on!

### ASCA BLOOD CHEMISTRY ANALYZER

**The first "proven"**
**centrifugal random access**
**chemistry analyzer with a**
**3-year track record of**
**uncommon accuracy**
**and reliability**

ASCA can perform more than 70 chemistry tests including thyroids, drugs and special chemistries with any number of 36 general chemistry methodologies performed simultaneously.

- Low initial cost.
- Re-usable 40-place carousel.
- Average test cost of 8¢!
- Over 70 chemistries available.
- 480 end points or 400 kinetics per hour in the batch mode.
- Batch, Stat or Profile modes with results in less than 8 minutes.

Call DLC Diagnostics • California/Nevada Distributors
In California **(800) 858-3889** • Out-Of-State Call Collect **(213) 602-2184**
7008 Marcelle Street • Paramount, California 90723

# Rocephin® IV·IM

## ceftriaxone sodium/Roche

**Before prescribing, please consult complete product information, a summary of which follows**

*MICROBIOLOGY* The bactericidal activity of ceftriaxone results from inhibition of cell wall synthesis. Ceftriaxone has a high degree of stability in the presence of beta lactamases, both penicillinases and cephalosporinases, of gram-negative and gram-positive bacteria. Ceftriaxone is usually active against the following microorganisms *in vitro* and in clinical infections (see Indications and Usage)

*GRAM-NEGATIVE AEROBES: Enterobacter aerogenes, Enterobacter cloacae, Escherichia coli, Haemophilus influenzae* (including ampicillin-resistant strains), *H parainfluenzae, Klebsiella* species (including *K pneumoniae*), *Neisseria gonorrhoeae* (including penicillinase and nonpenicillinase producing strains), *Neisseria meningitidis, Proteus mirabilis, Proteus vulgaris, Morganella morganii* and *Serratia marcescens*

Note: Many strains of the above organisms that are multiply resistant to other antibiotics e.g. penicillins, cephalosporins and aminoglycosides, are susceptible to ceftriaxone sodium

Ceftriaxone is also active against many strains of *Pseudomonas aeruginosa*

*GRAM-POSITIVE AEROBES: Staphylococcus aureus* (including penicillinase producing strains) and *Staphylococcus epidermidis* (Note: methicillin resistant staphylococci are resistant to cephalosporins, including ceftriaxone), *Streptococcus pyogenes* (Group A beta hemolytic streptococci), *Streptococcus agalactiae* (Group B streptococci) and *Streptococcus pneumoniae* (Note: Most strains of enterococci, *Streptococcus faecalis* and Group D streptococci are resistant.)

Ceftriaxone also demonstrates *in vitro* activity against the following microorganisms, although the clinical significance is unknown

*GRAM-NEGATIVE AEROBES: Citrobacter freundii, Citrobacter diversus, Providencia* species (including *Providencia rettgeri*), *Salmonella* species (including *S typhi*), *Shigella* species and *Acinetobacter calcoaceticus*

*ANAEROBES: Bacteroides* species, *Clostridium* species (Note: most strains of *C difficile* are resistant)

*SUSCEPTIBILITY TESTING* Standard susceptibility disk method. Quantitative methods that require measurement of zone diameters give the most precise estimate of antibiotic susceptibility. One such procedure (Bauer AW, Kirby WMM, Sherris JC, Turck M: Antibiotic Susceptibility Testing by a Standardized Single Disk Method, *Am J Clin Pathol* 45: 493-496, 1966; Standardized Disk Susceptibility Test, *Federal Register* 39: 19182-19184, 1974, National Committee for Clinical Laboratory Standards, Approved Standard ASM 2, Performance Standards for Antimicrobial Disk Susceptibility Tests, July 1975) has been recommended for use with disks to test susceptibility to ceftriaxone.

Laboratory results of the standardized single-disk susceptibility test using a 30-mcg ceftriaxone disk should be interpreted according to the following three criteria:

1. Susceptible organisms produce zones of 18 mm or greater, indicating that the tested organism is likely to respond to therapy.
2. Organisms that produce zones of 14 to 17 mm are expected to be susceptible if a high dosage (not to exceed 4 gm per day) is used or if the infection is confined to tissues and fluids (e.g., urine) in which high antibiotic levels are attained.
3. Resistant organisms produce zones of 13 mm or less, indicating that other therapy should be selected.

Organisms should be tested with the ceftriaxone disk, since ceftriaxone has been shown by *in vitro* tests to be active against certain strains found resistant to cephalosporin class disks.

Organisms having zones of less than 18 mm around the cephalothin disk are not necessarily of intermediate susceptibility or resistant to ceftriaxone.

Standardized procedures require use of control organisms. The 30-mcg ceftriaxone disk should give zone diameters between 29 and 35 mm, 22 and 28 mm and 17 and 23 mm for the reference strains *E coli* ATCC 25922, *S aureus* ATCC 25923 and *P aeruginosa* ATCC 27853, respectively.

*DILUTION TECHNIQUES*: Based on the pharmacokinetic profile of ceftriaxone, a bacterial isolate may be considered susceptible if the MIC value for ceftriaxone is not more than 16 mcg/ml. Organisms are considered resistant to ceftriaxone if the MIC is equal to or greater than 64 mcg/ml. Organisms having an MIC value of less than 64 mcg/ml, but greater than 16 mcg/ml, are expected to be susceptible if a high dosage (not to exceed 4 gm per day) is used or if the infection is confined to tissues and fluids (e.g., urine), in which high antibiotic levels are attained.

*E coli* ATCC 25922, *S aureus* ATCC 25923 and *P aeruginosa* ATCC 27853 are also the recommended reference strains for controlling ceftriaxone dilution tests. Greater than 95% of MICs for the *E coli* strain should fall within the range of 0.016 to 0.5 mcg/ml. The range for the *S aureus* strain should be 1 to 2 mcg/ml, while for the *P aeruginosa* strain the range should be 8 to 64 mcg/ml.

**INDICATIONS AND USAGE:** Rocephin is indicated for the treatment of the following infections when caused by susceptible organisms:

*LOWER RESPIRATORY TRACT INFECTIONS* caused by *Strep pneumoniae, Streptococcus* species (excluding enterococci), *Staph aureus, H influenzae, H parainfluenzae, Klebsiella* species (including *K pneumoniae*), *E coli, E aerogenes, Proteus mirabilis* and *Serratia marcescens*

*SKIN AND SKIN STRUCTURE INFECTIONS* caused by *Staph aureus, Staph epidermidis, Streptococcus* species (excluding enterococci), *E cloacae, Klebsiella* species (including *K pneumoniae*), *Proteus mirabilis* and *Pseudomonas aeruginosa*

*URINARY TRACT INFECTIONS (complicated and uncomplicated)* caused by *E coli, Proteus mirabilis, Proteus vulgaris, M morganii* and *Klebsiella* species (including *K pneumoniae*)

*UNCOMPLICATED GONORRHEA (cervical/urethral and rectal)* caused by *Neisseria gonorrhoeae*, including both penicillinase and nonpenicillinase producing strains

*PELVIC INFLAMMATORY DISEASE* caused by *N gonorrhoeae*

*BACTERIAL SEPTICEMIA* caused by *Staph aureus, Strep pneumoniae, E coli, H influenzae* and *K pneumoniae*

*BONE AND JOINT INFECTIONS* caused by *Staph aureus, Strep pneumoniae, Streptococcus* species (excluding enterococci), *E coli, P mirabilis, K pneumoniae* and *Enterobacter* species

*INTRA-ABDOMINAL INFECTIONS* caused by *E coli* and *K pneumoniae*

*MENINGITIS* caused by *H influenzae, N meningitidis* and *Strep pneumoniae*. Ceftriaxone has also been used successfully in a limited number of cases of meningitis and shunt infections caused by *Staph epidermidis* and *E coli*.

*PROPHYLAXIS*: The administration of a single dose of ceftriaxone preoperatively may reduce the incidence of postoperative infections in patients undergoing coronary artery bypass surgery.

Although ceftriaxone has been shown to have been as effective as cefazolin in the prevention of infection following coronary artery bypass surgery, no placebo-controlled trials have been conducted to evaluate any cephalosporin antibiotic in the prevention of infection following coronary artery bypass surgery.

*SUSCEPTIBILITY TESTING*: Before instituting treatment with Rocephin, appropriate specimens should be obtained for isolation of the causative organism and for determination of its susceptibility to the drug. Therapy may be instituted prior to obtaining results of susceptibility testing.

**CONTRAINDICATIONS:** Rocephin is contraindicated in patients with known allergy to the cephalosporin class of antibiotics.

**WARNINGS:** BEFORE THERAPY WITH ROCEPHIN IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE TO DETERMINE WHETHER THE PATIENT HAS HAD PREVIOUS HYPERSENSITIVITY REACTIONS TO CEPHALOSPORINS, PENICILLINS OR OTHER DRUGS. THIS PRODUCT SHOULD BE GIVEN CAUTIOUSLY TO PENICILLIN-SENSITIVE PATIENTS. ANTIBIOTICS SHOULD BE ADMINISTERED WITH CAUTION TO ANY PATIENT WHO HAS DEMONSTRATED SOME FORM OF ALLERGY, PARTICULARLY TO DRUGS. SERIOUS ACUTE HYPERSENSITIVITY REACTIONS MAY REQUIRE THE USE OF SUBCUTANEOUS EPINEPHRINE AND OTHER EMERGENCY MEASURES.

Pseudomembranous colitis has been reported with the use of cephalosporins (and other broad spectrum antibiotics), therefore, it is important to consider its diagnosis in patients who develop diarrhea in association with antibiotic use.

**ROCEPHIN® (ceftriaxone sodium/Roche)**

Treatment with broad spectrum antibiotics alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate a toxin produced by *Clostridium difficile* is one primary cause of antibiotic associated colitis. Cholestyramine and colestipol resins have been shown to bind to the toxin *in vitro*.

Mild cases of colitis respond to drug discontinuance alone. Moderate to severe cases should be managed with fluid, electrolyte and protein supplementation as indicated.

When the colitis is not relieved by drug discontinuance or when it is severe, oral vancomycin is the treatment of choice for antibiotic-associated pseudomembranous colitis produced by *C difficile*. Other causes of colitis should also be considered.

**PRECAUTIONS** *GENERAL*: Although transient elevations of BUN and serum creatinine have been observed, at the recommended dosages, the nephrotoxic potential of Rocephin is similar to that of other cephalosporins.

Ceftriaxone is excreted via both biliary and renal excretion (see Clinical Pharmacology). Therefore, patients with renal failure normally require no adjustment in dosage when usual doses of Rocephin are administered, but concentrations of drug in the serum should be monitored periodically. If evidence of accumulation exists, dosage should be decreased accordingly.

Dosage adjustments should not be necessary in patients with hepatic dysfunction, however, in patients with both hepatic dysfunction and significant renal disease, Rocephin dosage should not exceed 2 gm daily without close monitoring of serum concentrations.

Alterations in prothrombin times have occurred rarely in patients treated with Rocephin. Patients with impaired vitamin K synthesis or low vitamin K stores (e.g., chronic hepatic disease and malnutrition) may require monitoring of prothrombin time during Rocephin treatment. Vitamin K administration (10 mg weekly) may be necessary if the prothrombin time is prolonged before or during therapy.

Prolonged use of Rocephin may result in overgrowth of nonsusceptible organisms. Careful observation of the patient is essential. If superinfection occurs during therapy, appropriate measures should be taken.

Rocephin should be prescribed with caution in individuals with a history of gastrointestinal disease, especially colitis.

*CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY*: Carcinogenesis: Considering the maximum duration of treatment and the class of the compound, carcinogenicity studies with ceftriaxone in animals have not been performed. The maximum duration of animal toxicity studies was six months.

Mutagenesis: Genetic toxicology tests included the Ames test, a micronucleus test and a test for chromosomal aberrations in human lymphocytes cultured *in vitro* with ceftriaxone. Ceftriaxone showed no potential for mutagenic activity in these studies.

Impairment of Fertility: Ceftriaxone produced no impairment of fertility when given intravenously to rats at daily doses up to 586 mg/kg/day, approximately 20 times the recommended clinical dose of 2 gm/day.

*PREGNANCY*: Teratogenic Effects: Pregnancy Category B. Reproductive studies have been performed in mice and rats at doses up to 20 times the usual human dose and have no evidence of embryotoxicity, fetotoxicity or teratogenicity. In primates, no embryotoxicity or teratogenicity was demonstrated at a dose approximately three times the human dose.

There are, however, no adequate and well controlled studies in pregnant women. Because animal reproductive studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nonteratogenic Effects: In rats, in the Segment I (fertility and general reproduction) and Segment III (perinatal and postnatal) studies with intravenously administered ceftriaxone, no adverse effects were noted on various reproductive parameters during gestation and lactation, including postnatal growth, functional behavior and reproductive ability of the offspring, at doses of 586 mg/kg/day or less.

*NURSING MOTHERS*: Low concentrations of ceftriaxone are excreted in human milk. Caution should be exercised when Rocephin is administered to a nursing woman.

*PEDIATRIC USE*: Safety and effectiveness of Rocephin in neonates, infants and children have been established for the dosages described in the Dosage and Administration section.

**ADVERSE REACTIONS:** Rocephin is generally well tolerated. In clinical trials, the following adverse reactions, which were considered to be related to Rocephin therapy or of uncertain etiology, were observed:

*LOCAL REACTIONS*—pain, induration or tenderness at the site of injection (1%). Less frequently reported (less than 1%) was phlebitis after I.V. administration.

*HYPERSENSITIVITY*—rash (1.7%). Less frequently reported (less than 1%) were pruritus, fever or chills.

*HEMATOLOGIC*—eosinophilia (6%), thrombocytosis (5.1%) and leukopenia (2.1%). Less frequently reported (less than 1%) were anemia, neutropenia, lymphopenia, thrombocytopenia and prolongation of the prothrombin time.

*GASTROINTESTINAL*—diarrhea (2.7%). Less frequently reported (less than 1%) were nausea or vomiting, and dysgeusia.

*HEPATIC*—elevations of SGOT (3.1%) or SGPT (3.3%). Less frequently reported (less than 1%) were elevations of alkaline phosphatase and bilirubin.

*RENAL*—elevations of the BUN (1.2%). Less frequently reported (less than 1%) were elevations of creatinine and the presence of casts in the urine.

*CENTRAL NERVOUS SYSTEM*: headache or dizziness were reported occasionally (less than 1%).

*GENITOURINARY*—moniliasis or vaginitis were reported occasionally (less than 1%).

*MISCELLANEOUS*—diaphoresis and flushing were reported occasionally (less than 1%).

Other rarely observed adverse reactions (less than 0.1%) include leukocytosis, lymphocytosis, monocytosis, basophilia, a decrease in the prothrombin time, jaundice, glycosuria, hematuria, bronchospasm, serum sickness, abdominal pain, colitis, flatulence, dyspepsia, palpitations and epistaxis.

**DOSAGE AND ADMINISTRATION:** Rocephin may be administered intravenously or intramuscularly. The usual adult daily dose is 1 to 2 gm given once a day (or in equally divided doses twice a day) depending on the type and severity of the infection. The total daily dose should not exceed 4 grams.

For the treatment of serious miscellaneous infections in children, other than meningitis, the recommended total daily dose is 50 to 75 mg/kg (not to exceed 2 grams) given in divided doses every 12 hours. Generally, Rocephin therapy should be continued for at least two days after the signs and symptoms of infection have disappeared. The usual duration is 4 to 14 days, in complicated infections longer therapy may be required.

In the treatment of meningitis, a daily dose of 100 mg/kg (not to exceed 4 grams), given in divided doses every 12 hours, should be administered with or without a loading dose of 75 mg/kg.

For the treatment of uncomplicated gonococcal infections, a single intramuscular dose of 250 mg is recommended.

For preoperative use (surgical prophylaxis), a single dose of 1 gm administered ½ to 2 hours before surgery is recommended.

When treating infections caused by *Streptococcus pyogenes*, therapy should be continued for at least ten days.

No dosage adjustment is necessary for patients with impairment of renal or hepatic function; however, blood levels should be monitored in patients with severe renal impairment (*e.g.*, dialysis patients) and in patients with both renal and hepatic dysfunctions.

**HOW SUPPLIED:** Rocephin (ceftriaxone sodium/Roche) is supplied as a sterile crystalline powder in glass vials and piggyback bottles. The following packages are available:

Vials containing 250 mg equivalent of ceftriaxone. Boxes of 10 (NDC 0004-1962-01)

Vials containing 500 mg equivalent of ceftriaxone. Boxes of 10 (NDC 0004-1963-01)

Vials containing 1 gm equivalent of ceftriaxone. Boxes of 10 (NDC 0004-1964-01)

Piggyback bottles containing 1 gm equivalent of ceftriaxone. Boxes of 10 (NDC 0004-1964-03)

Vials containing 2 gm equivalent of ceftriaxone. Boxes of 10 (NDC 0004-1965-01)

Piggyback bottles containing 2 gm equivalent of ceftriaxone. Boxes of 10 (NDC 0004-1965-03)

Bulk pharmacy containers, containing 10 gm equivalent of ceftriaxone. Boxes of 1 (NDC 0004-1971-01)

NOT FOR DIRECT ADMINISTRATION.

Roche Laboratories
Division of Hoffmann-La Roche Inc.
Nutley, New Jersey 07110

ROCHE®

# Mean,

Powerful against susceptible pathogens.*

# lean &

Easy on tight budgets.

# clean.

Gentle to patients (generally well tolerated).

The one antimicrobial that belongs on every formulary.

## Once-a-day

# Rocephin® ROCHE IV·IM

## ceftriaxone sodium/Roche

* ROCEPHIN is indicated in the following infections: bacterial septicemia, bone and joint, intra-abdominal, lower respiratory tract, skin and skin structure, urinary tract, bacterial meningitis and gonorrhea. Please see summary of product information on adjacent page for indicated susceptible organisms.

Copyright © 1987 by Hoffmann-La Roche Inc. All rights reserved

Please see adjacent page for summary of product information.

INCORPORATING
ARIZONA MEDICINE
SEE PAGE 694

# The Western Journal of Medicine

VOLUME 146 • NUMBER 6 JUNE 1987


### CLINICAL INVESTIGATION

695 Clorazepate Use May Prevent Alcohol Withdrawal Convulsions
V G HADDOX, T G BIDDER, L E WALDRON, P DERBY and S M W ACHEN

### CLINICAL MEDICINE

697 Increased Use of Medical Services and Antibiotics by Children Who Claim a Prior Penicillin Sensitivity
M J KRAEMER, H CAPRYE-BOOS and H S BERMAN

701 Treatment of Severe Hypertension and Hypertensive Crises With Nifedipine
M C HOUSTON

### MEDICAL PROGRESS

705 Treatable Dementias
M E MAHLER, J L CUMMINGS and D F BENSON

### SPECIALTY CONFERENCE

713 Cardiac Ischemia. Part I—Metabolic and Physiologic Responses
Moderator: G A LANGER
Discussants: J N WEISS and H R SCHELBERT

### MEDICAL STAFF CONFERENCE

724 Peptic Ulcer Disease—Pathophysiology and Current Medical Management
Discussant: B F SCHARSCHMIDT

### EPITOMES

734 Important Advances in General Surgery

### EDITORIALS

740 Contemporary Aims for American Medicine • Differentiating Treatable Causes of Dementia

### CASE REPORTS

742 Reversible Renal Resistance to Aldosterone Associated With Interstitial Nephritis
J J REGAN, Jr, C S GREENBERG, A D MOORADIAN, N STALEY, F Q NUTTALL

745 Sarcoidosis and Pheochromocytoma
K M MURRAY and R F SCHILLACI

### CORRESPONDENCE

748 Management of Lumbar Disc Disease • Infection Associated With Joystick Mimicking a Spider Bite • The Elusiveness of Truth • Wright's Law • Dollar Mentality • Cultural Change, Social Disintegration and Medicine• Importance of Dive Tables in Scuba Diving

### TOPICS IN PRIMARY CARE MEDICINE

751 A Clinician's Guide to Helping Patients Change Behavior
A R MARTIN and T J COATES

### FORUM

754 Contemporary Aims for American Medicine—1987—A Report on a Forum
M S M WATTS

### COMMENTARY

759 Fear of the Unknown
E R W FOX

### INFORMATION

761 Use and Safety of Antimicrobial Agents During Pregnancy
A W CHOW and P J JEWESSON

765 Leaving a Cardiology Service Against Medical Advice—A Follow-Up Study
H N OCHITILL, R C BYRD and J GREENE

### OTHER FEATURES

681 Subscription Information

688 Continuing Medical Education Activities in Arizona; California, Hawaii and Nevada; Idaho; Montana; New Mexico; Utah; Washington; Wyoming

766 Volume Index

778 Classified Advertising

780 In Memoriam

793 Wyoming Medical Society Annual Meeting

801 Idaho Medical Association Annual Meeting

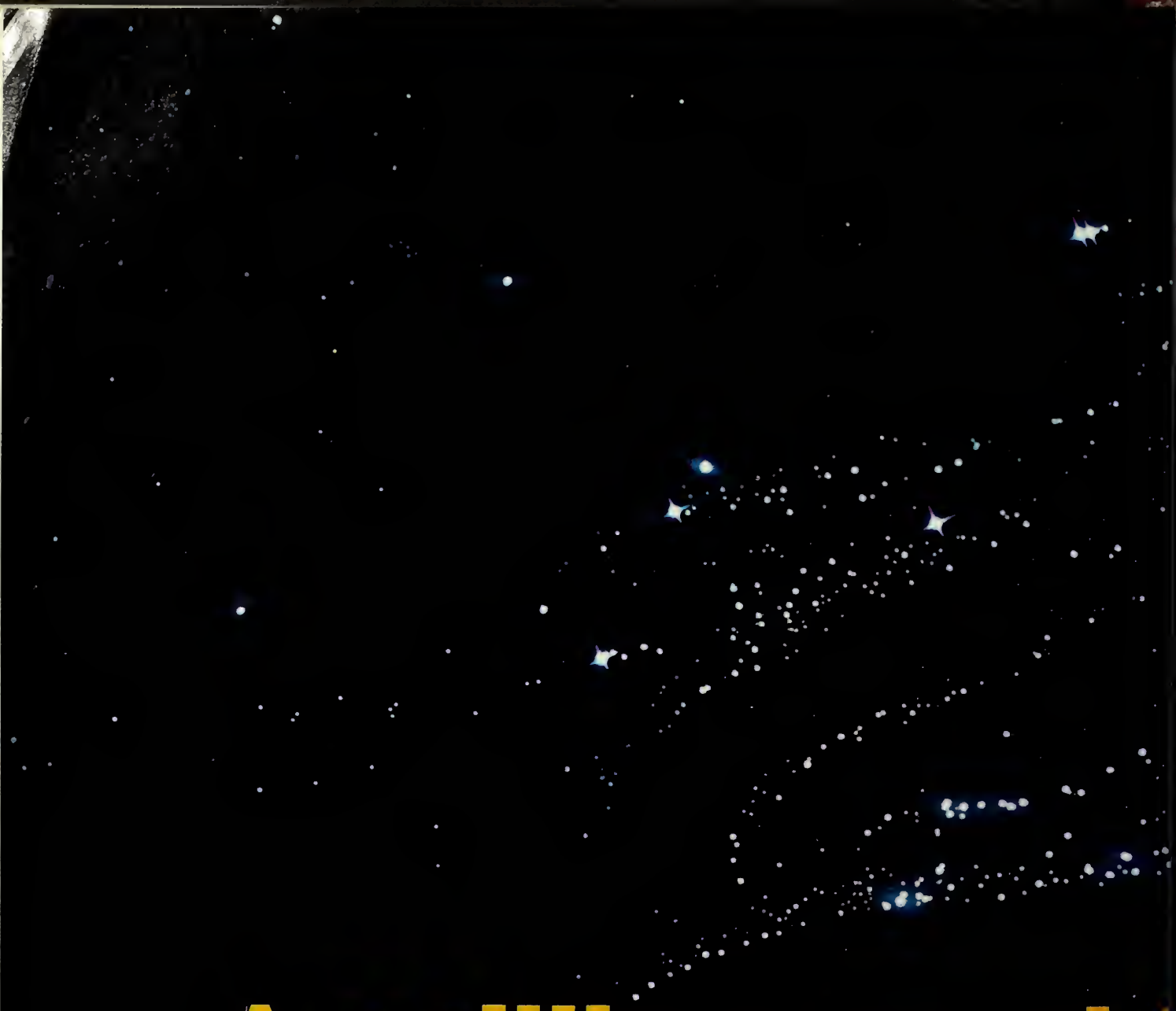
806 Western State Medical Associations' Meetings

**Detailed Table of Contents:** 667, 671, 672


THE FRANCIS A. COUNTWAY LIBRARY OF MEDICINE BOSTON, MA
JUN 19 1987

Official Journal of the Arizona Medical Association, the California Medical Association, the Idaho Medical Association, the Montana Medical Association, the Nevada State Medical Association, the New Mexico Medical Society, the Utah State Medical Association, the Washington State Medical Association and the Wyoming Medical Society. Affiliated Specialty Society: California Society of Internal Medicine.

Affiliated Clinical Investigation Societies: the Western Association of Physicians; the Western Society for Clinical Investigation; the Western Section, American Federation for Clinical Research; the Western Society for Pediatric Research; the Western Region, Society for Investigative Dermatology.



# A million and 1

## A poetic understatement

The actual number is in the billions. For more than 15 years, Dalmane (flurazepam HCl/Roche) has been providing sleep that satisfies patients—sleep that comes quickly and lasts through the night.[1-8]

Sleep that satisfies *you*—you can count on an exceptionally wide margin of safety.[7-9] As always, caution patients about driving or drinking alcohol.

ROCHE®

Copyright © 1986 by Roche Products Inc. All rights reserved

# nights of sleep...

## DALMANE®

brand of
flurazepam HCl/Roche Ⓒ IV

## sleep that satisfies

Please see adjacent page for references and summary of product information

References: 1. Koles J, *et al. Clin Pharmacol Ther* 12:691-697, Jul-Aug 1971. 2. Koles A, *et al. Clin Pharmacol Ther* 18:356-363, Sep 1975. 3. Koles A, *et al: Clin Pharmacol Ther* 19:576-583, May 1976. 4. Koles A, *et al. Clin Pharmacol Ther* 32:781-788, Dec 1982. 5. Frost JD Jr, DeLucchi MR. *J Am Geriatr Soc* 27:541-546, Dec 1979. 6. Dement WC, *et al: Behav Med*, pp 25-31, Oct 1978. 7. Koles A, Koles JD: *J Clin Psychopharmacol* 3:140-150, Apr 1983. 8. Tennant FS, *et al:* Symposium on the Treatment of Sleep Disorders, Teleconference, Oct 16, 1984. 9. Greenblott DJ, Allen MD, Shoder RI. *Clin Pharmacol Ther* 21:355-361, Mar 1977.

**DALMANE®**
brand of
flurazepam HCl/Roche ®
**sleep that satisfies**

15-mg/30-mg capsules

**Before prescribing, please consult complete product information, a summary of which follows:**
**Indications:** Effective in all types of insomnia characterized by difficulty in falling asleep, frequent nocturnal awakenings and/or early morning awakening; in patients with recurring insomnia or poor sleeping habits, in acute or chronic medical situations requiring restful sleep. Objective sleep laboratory data have shown effectiveness for at least 28 consecutive nights of administration. Since insomnia is often transient and intermittent, prolonged administration is generally not necessary or recommended. Repeated therapy should only be undertaken with appropriate patient evaluation.
**Contraindications:** Known hypersensitivity to flurazepam HCl; pregnancy. Benzodiazepines may cause fetal damage when administered during pregnancy. Several studies suggest an increased risk of congenital malformations associated with benzodiazepine use during the first trimester. Warn patients of the potential risks to the fetus should the possibility of becoming pregnant exist while receiving flurazepam. Instruct patients to discontinue drug prior to becoming pregnant. Consider the possibility of pregnancy prior to instituting therapy.
**Warnings:** Caution patients about possible combined effects with alcohol and other CNS depressants. An additive effect may occur if alcohol is consumed the day following use for nighttime sedation. This potential may exist for several days following discontinuation. Caution against hazardous occupations requiring complete mental alertness (*e.g.*, operating machinery, driving). Potential impairment of performance of such activities may occur the day following ingestion. Not recommended for use in persons under 15 years of age. Withdrawal symptoms rarely reported; abrupt discontinuation should be avoided with gradual tapering of dosage for those patients on medication for a prolonged period of time. Use caution in administering to addiction-prone individuals or those who might increase dosage.
**Precautions:** In elderly and debilitated patients, it is recommended that the dosage be limited to 15 mg to reduce risk of oversedation, dizziness, confusion and/or ataxia. Consider potential additive effects with other hypnotics or CNS depressants. Employ usual precautions in severely depressed patients, or in those with latent depression or suicidal tendencies, or in those with impaired renal or hepatic function.
**Adverse Reactions:** Dizziness, drowsiness, lightheadedness, staggering, ataxia and falling have occurred, particularly in elderly or debilitated patients. Severe sedation, lethargy, disorientation and coma, probably indicative of drug intolerance or overdosage, have been reported. Also reported: headache, heartburn, upset stomach, nausea, vomiting, diarrhea, constipation, GI pain, nervousness, talkativeness, apprehension, irritability, weakness, palpitations, chest pains, body and joint pains and GU complaints. There have also been rare occurrences of leukopenia, granulocytopenia, sweating, flushes, difficulty in focusing, blurred vision, burning eyes, faintness, hypotension, shortness of breath, pruritus, skin rash, dry mouth, bitter taste, excessive salivation, anorexia, euphoria, depression, slurred speech, confusion, restlessness, hallucinations, and elevated SGOT, SGPT, total and direct bilirubins, and alkaline phosphatase, and paradoxical reactions, *e.g.*, excitement, stimulation and hyperactivity.
**Dosage:** Individualize for maximum beneficial effect. *Adults:* 30 mg usual dosage; 15 mg may suffice in some patients. *Elderly or debilitated patients:* 15 mg recommended initially until response is determined.
**Supplied:** Capsules containing 15 mg or 30 mg flurazepam HCl.

ROCHE®
Roche Products Inc
Manati, Puerto Rico 00701



When you find yourself spending more time marketing your private practice, collecting receivables and hiring/training office personnel than you are able to spend seeing patients, perhaps it's time to explore career opportunities with **GENERAL MED.**

And when you find your malpractice insurance, benefits for you and your employees and office expenses cutting further into your profits, perhaps it's time to explore career opportunities with **GENERAL MED.**

**GENERAL MED** is an HMO serving the Southern California counties of Orange, Los Angeles, San Bernardino, Riverside and San Diego. We handle the entire business end of a medical practice. In addition, we offer a very competitive salary and excellent benefits—including employer paid malpractice, comprehensive health benefits, life insurance, disability insurance, vacation, CME time and a 401k plan.

It has been said that Health Maintenance Organizations are the "wave of the future." Why not "catch the wave" with **GENERAL MED.**

If you are Board certified (or eligible) in your specialty (including Family Practice) and possess a California license, please send your CV to:

Nancy Boostrom
Physician Recruiter

GeneralMed
701 South Parker Street, Suite 5000
Orange, California 92668

***The Western Journal of Medicine***
(ISSN 0093-0415/USPS 084 480) is published monthly for $30 per year (USA and Canada) by the California Medical Association, 44 Gough Street, San Francisco, CA 94103. Second-class postage paid at San Francisco, CA and additional mailing offices.
**POSTMASTER:** Send address changes to *The Western Journal of Medicine*, Circulation, P.O. Box 7602, San Francisco, CA 94120-7602.

# *Moving?*

Please give us six weeks notice and supply your personal reference number.

ID No.

The Western Journal of Medicine
P.O. Box 7602
San Francisco, CA 94120-7602.

302703 XX

**The Western Journal of Medicine**

P.O. Box 7602, San Francisco, CA 94120-7602

# DEPAKOTE®

## DIVALPROEX SODIUM ENTERIC-COATED TABLETS

**All the advantages of Depakene® (valproic acid) plus improved gastrointestinal tolerance**

# NOW ON MEDI-CAL FORMULARY

Medi-Cal Numbers:

(Actual size)

500 mg

**2414D**
**500 mg**

(Actual size)

250 mg

**2414A**
**250 mg**

(Actual size)

125 mg

NO. PENDING
**125 mg**

Please see adjoining page for prescribing information.

Abbott Laboratories, North Chicago, IL60064

# DEPAKOTE®

## DIVALPROEX SODIUM
## ENTERIC-COATED TABLETS

## NOW ON MEDI-CAL FORMULARY

**WARNING**
HEPATIC FAILURE RESULTING IN FATALITIES HAS OCCURRED IN PATIENTS RECEIVING VALPROIC ACID AND ITS DERIVATIVES EXPERIENCE HAS INDICATED THAT CHILDREN UNDER THE AGE OF TWO YEARS ARE AT A CONSIDERABLY INCREASED RISK OF DEVELOPING FATAL HEPATOTOXICITY ESPECIALLY THOSE ON MULTIPLE ANTICONVULSANTS, THOSE WITH CONGENITAL METABOLIC DISORDERS, THOSE WITH SEVERE SEIZURE DISORDERS ACCOMPANIED BY MENTAL RETARDATION, AND THOSE WITH ORGANIC BRAIN DISEASE WHEN DEPAKOTE IS USED IN THIS PATIENT GROUP, IT SHOULD BE USED WITH EXTREME CAUTION AND AS A SOLE AGENT THE BENEFITS OF SEIZURE CONTROL SHOULD BE WEIGHED AGAINST THE RISKS ABOVE THIS AGE GROUP, EXPERIENCE HAS INDICATED THAT THE INCIDENCE OF FATAL HEPATOTOXICITY DECREASES CONSIDERABLY IN PROGRESSIVELY OLDER PATIENT GROUPS

THESE INCIDENTS USUALLY HAVE OCCURRED DURING THE FIRST SIX MONTHS OF TREATMENT SERIOUS OR FATAL HEPATOTOXICITY MAY BE PRECEDED BY NON-SPECIFIC SYMPTOMS SUCH AS LOSS OF SEIZURE CONTROL, MALAISE, WEAKNESS, LETHARGY, FACIAL EDEMA, ANOREXIA AND VOMITING PATIENTS SHOULD BE MONITORED CLOSELY FOR APPEARANCE OF THESE SYMPTOMS LIVER FUNCTION TESTS SHOULD BE PERFORMED PRIOR TO THERAPY AND AT FREQUENT INTERVALS THEREAFTER, ESPECIALLY DURING THE FIRST SIX MONTHS

**DESCRIPTION**: Divalproex sodium is a stable coordination compound comprised of sodium valproate and valproic acid in a 1 1 molar relationship and formed during the partial neutralization of valproic acid with DS equivalent of sodium hydroxide Chemically it is designated as sodium hydrogen bis(2 propylpentanoate)

Divalproex sodium has a molecular weight of 310 41 and occurs as a white powder with a characteristic odor

DEPAKOTE is an oral antiepileptic supplied as enteric-coated tablets in three dosage strengths containing divalproex sodium equivalent to 125 mg, 250 mg or 500 mg of valproic acid

**Inactive Ingredients**
f25 mg tablets cellulosic polymers, diacetylated monoglycerides, FD&C Blue No 1, FD&C Red No 40 povidone pregelatinized starch (contains corn starch), silica gel, talc titanium dioxide vanillin and other ingredients

250 mg tablets cellulosic polymers diacetylated monoglycerides, FD&C Yellow No 6, iron oxide povidone pregelatinized starch (contains corn starch), silica gel, talc, titanium dioxide vanillin and other ingredients

500 mg tablets cellulosic polymers, diacetylated monoglycerides D&C Red No 30, FD&C Blue No 2 iron oxide povidone, pregelatinized starch (contains corn starch), silica gel, talc, titanium dioxide vanillin and other ingredients

**CLINICAL PHARMACOLOGY**: DEPAKOTE is an antiepileptic agent which is chemically related to valproic acid It has no nitrogen or aromatic moiety characteristic of other antiepileptic drugs The mechanism by which DEPAKOTE exerts its antiepileptic effects has not been established It has been suggested that its activity is related to increased brain levels of gamma aminobutyric acid (GABA) The effect on the neuronal membrane is unknown DEPAKOTE dissociates into valproate in the gastrointestinal tract

Because of the enteric coating of DEPAKOTE absorption is delayed one hour following oral administration Thereafter, DEPAKOTE is uniformly and reliably absorbed, as shown by studies in normal volunteers Peak serum levels of valproate occur in 3 to 4 hours Bioavailability of divalproex sodium tablets was found to be equivalent to that of DEPAKENE® (valproic acid) capsules Concomitant administration with food would be expected to slow absorption but not affect the extent of absorption The serum half life of valproate is typically in the range of six to sixteen hours Half-lives in the lower part of the above range are usually found in patients taking other antiepileptic drugs capable of enzyme induction

Enteric-coated divalproex sodium may reduce the incidence of the irritative gastrointestinal effects of valproate as compared to valproic acid capsules

Valproate is rapidly distributed and at therapeutic drug concentrations, drug is highly bound (90%) to human plasma proteins Increases in dose may result in decreases in the extent of protein binding and increased valproate clearance and elimination

Elimination of DEPAKOTE and its metabolites occurs principally in the urine with minor amounts in the feces and expired air Very little unmetabolized parent drug is excreted in the urine The drug is primarily metabolized in the liver and is excreted as the glucuronide conjugate Other metabolites in the urine are products of beta, omega 1, and omega oxidation (C 3, C 4 and C 5 positions) The major oxidative metabolite in the urine is 2 propyl 3 keto-pentanoic acid, minor metabolites are 2 propyl glutaric acid, 2 propyl 5 hydroxypentanoic acid 2 propyl 3-hydroxypentanoic acid and 2 propyl 4 hydroxypentanoic acid

**INDICATIONS AND USAGE**: DEPAKOTE (divalproex sodium) is indicated for use as sole and adjunctive therapy in the treatment of simple (petit mal) and complex absence seizures DEPAKOTE may also be used adjunctively in patients with multiple seizure types which include absence seizures

In accordance with the International Classification of Seizures, simple absence is defined as very brief clouding of the sensorium or loss of consciousness (lasting usually 2-15 seconds) accompanied by certain generalized epileptic discharges without other detectable clinical signs Complex absence is the term used when other signs are also present

SEE "WARNINGS" SECTION FOR STATEMENT REGARDING FATAL HEPATIC DYSFUNCTION

**CONTRAINDICATIONS**: DEPAKOTE (DIVALPROEX SODIUM) SHOULD NOT BE ADMINISTERED TO PATIENTS WITH HEPATIC DISEASE OR SIGNIFICANT DYSFUNCTION

DEPAKOTE is contraindicated in patients with known hypersensitivity to the drug

**WARNINGS**: **Hepatic failure resulting in fatalities has occurred in patients receiving valproic acid. These incidents usually have occurred during the first six months of treatment. Serious or fatal hepatotoxicity may be preceded by non-specific symptoms such as loss of seizure control, malaise, weakness, lethargy, facial edema, anorexia and vomiting. Patients should be monitored closely for appearance of these symptoms. Liver function tests should be performed prior to therapy and at frequent intervals thereafter, especially during the first six months. However, physicians should not rely totally on serum biochemistry since these tests may not be abnormal in all instances, but should also consider the results of careful interim medical history and physical examination. Caution should be observed when administering DEPAKOTE to patients with a prior history of hepatic disease. Patients on multiple anticonvulsants, children, those with congenital metabolic disorders, those with severe seizure disorders accompanied by mental retardation, and those with organic brain disease may be at particular risk. Experience has indicated that children under the age of two years are at a considerably increased risk of developing fatal hepatotoxicity, especially those with the aforementioned conditions. When DEPAKOTE is used in this patient group, it should be used with extreme caution and as a sole agent. The benefits of seizure control should be weighed against the risks. Above this age group, experience has indicated that the incidence of fatal hepatotoxicity decreases considerably in progressively older patient groups.**

**The drug should be discontinued immediately in the presence of significant hepatic dysfunction, suspected or apparent in some cases, hepatic dysfunction has progressed in spite of discontinuation of drug**

The frequency of adverse effects (particularly elevated liver enzymes) may be dose related The benefit of improved seizure control which may accompany the higher doses should therefore be weighed against the possibility of a greater incidence of adverse effects

*Usage in Pregnancy* ACCORDING TO PUBLISHED AND UNPUBLISHED REPORTS, VALPROIC ACID MAY PRODUCE TERATOGENIC EFFECTS IN THE OFFSPRING OF HUMAN FEMALES RECEIVING THE DRUG DURING PREGNANCY

THERE ARE MULTIPLE REPORTS IN THE CLINICAL LITERATURE WHICH INDICATE THAT THE USE OF ANTIEPILEPTIC DRUGS DURING PREGNANCY RESULTS IN AN INCREASED INCIDENCE OF BIRTH DEFECTS IN THE OFFSPRING ALTHOUGH DATA ARE MORE EXTENSIVE WITH RESPECT TO TRIMETHADIONE PARAMETHADIONE PHENYTOIN AND PHENOBARBITAL, REPORTS INDICATE A POSSIBLE SIMILAR ASSOCIATION WITH THE USE OF OTHER ANTIEPILEPTIC DRUGS THEREFORE, ANTIEPILEPTIC DRUGS SHOULD BE ADMINISTERED TO WOMEN OF CHILDBEARING POTENTIAL ONLY IF THEY ARE CLEARLY SHOWN TO BE ESSENTIAL IN THE MANAGEMENT OF THEIR SEIZURES

THE INCIDENCE OF NEURAL TUBE DEFECTS IN THE FETUS MAY BE INCREASED IN MOTHERS RECEIVING VALPROATE DURING THE FIRST TRIMESTER OF PREGNANCY THE CENTERS FOR DISEASE CONTROL (CDC) HAS ESTIMATED THE RISK OF VALPROIC ACID EXPOSED WOMEN HAVING CHILDREN WITH SPINA BIFIDA TO BE APPROXIMATELY 1 TO 2%[1] THIS RISK IS SIMILAR TO THAT FOR NONEPILEPTIC WOMEN WHO HAVE HAD CHILDREN WITH NEURAL TUBE DEFECTS (ANENCEPHALY AND SPINA BIFIDA)

ANIMAL STUDIES ALSO HAVE DEMONSTRATED VALPROIC ACID INDUCED TERATOGENICITY Studies in rats and human females demonstrated placental transfer of the drug Doses greater than 65 mg/kg/day given to pregnant rats and mice produced skeletal abnormalities in the offspring primarily involving ribs and vertebrae doses greater than 150 mg/kg day given to pregnant rabbits produced fetal resorptions and (primarily) soft tissue abnormalities in the offspring In rats a dose related delay in the onset of parturition was noted Postnatal growth and survival of the progeny were adversely affected, particularly when drug administration spanned the entire gestation and early lactation period

Antiepileptic drugs should not be discontinued in patients in whom the drug is administered to prevent major seizures because of the strong possibility of precipitating status epilepticus with attendant hypoxia and threat to life In individual cases where the severity and frequency of the seizure disorder are such that the removal of medication does not pose a serious threat to the patient, discontinuation of the drug may be considered prior to and during pregnancy, although it cannot be said with any confidence that even minor seizures do not pose some hazard to the developing embryo or fetus

The prescribing physician will wish to weigh these considerations in treating or counseling epileptic women of childbearing potential

**PRECAUTIONS**: *Hepatic Dysfunction* See "Boxed Warning," "Contraindications" and "Warnings" sections

*General* Because of reports of thrombocytopenia, inhibition of the secondary phase of platelet aggregation, and abnormal coagulation parameters, platelet counts and coagulation tests are recommended before initiating therapy and at periodic intervals It is recommended that patients receiving DEPAKOTE (divalproex sodium) be monitored for platelet count and coagulation parameters prior to planned surgery Evidence of hemorrhage, bruising or a disorder of hemostasis-coagulation is an indication for reduction of DEPAKOTE dosage or withdrawal of therapy

Hyperammonemia with or without lethargy or coma has been reported and may be present in the absence of abnormal liver function tests If clinically significant elevation occurs, DEPAKOTE should be discontinued

Since DEPAKOTE (divalproex sodium) may interact with concurrently administered antiepileptic drugs, periodic serum level determinations of concomitant antiepileptic drugs are recommended during the early course of therapy (See "Drug Interactions" section)

Valproate is partially eliminated in the urine as a keto metabolite which may lead to a false interpretation of the urine ketone test

There have been reports of altered thyroid function tests associated with valproate The clinical significance of these is unknown

*Information for Patients* Since DEPAKOTE may produce CNS depression, especially when combined with another CNS depressant (e.g., alcohol), patients should be advised not to engage in hazardous occupations, such as driving an automobile or operating dangerous machinery, until it is known that they do not become drowsy from the drug

*Drug Interactions* Valproic acid may potentiate the CNS depressant activity of alcohol

The concomitant administration of valproic acid with drugs that exhibit extensive protein binding (e.g., aspirin, carbamazepine, and dicumarol) may result in alteration of serum drug levels

THERE IS EVIDENCE THAT VALPROIC ACID CAN CAUSE AN INCREASE IN SERUM PHENOBARBITAL LEVELS BY IMPAIRMENT OF NON RENAL CLEARANCE THIS PHENOMENON CAN RESULT IN SEVERE CNS DEPRESSION THE COMBINATION OF VALPROIC ACID AND PHENOBARBITAL HAS ALSO BEEN REPORTED TO PRODUCE CNS DEPRESSION WITHOUT SIGNIFICANT ELEVATIONS OF BARBITURATE OR VALPROATE SERUM LEVELS ALL PATIENTS RECEIVING CONCOMITANT BARBITURATE THERAPY SHOULD BE CLOSELY MONITORED FOR NEUROLOGICAL TOXICITY SERUM BARBITURATE LEVELS SHOULD BE OBTAINED, IF POSSIBLE, AND THE BARBITURATE DOSAGE DECREASED, IF APPROPRIATE

Primidone is metabolized into a barbiturate and, therefore, may also be involved in a similar or identical interaction

THERE HAVE BEEN REPORTS OF BREAKTHROUGH SEIZURES OCCURRING WITH THE COMBINATION OF VALPROIC ACID AND PHENYTOIN MOST REPORTS HAVE NOTED A DECREASE IN TOTAL PLASMA PHENYTOIN CONCENTRATION HOWEVER, INCREASES IN TOTAL PHENYTOIN SERUM CONCENTRATION HAVE BEEN REPORTED AN INITIAL FALL IN TOTAL PHENYTOIN LEVELS WITH SUBSEQUENT INCREASE IN PHENYTOIN LEVELS HAS ALSO BEEN REPORTED IN ADDITION A DECREASE IN TOTAL SERUM PHENYTOIN WITH AN INCREASE IN THE FREE VS PROTEIN BOUND PHENYTOIN LEVELS HAS BEEN REPORTED THE DOSAGE OF PHENYTOIN SHOULD BE ADJUSTED AS REQUIRED BY THE CLINICAL SITUATION

THE CONCOMITANT USE OF VALPROIC ACID AND CLONAZEPAM MAY PRODUCE ABSENCE STATUS

There is inconclusive evidence regarding the effect of valproate on serum ethosuximide levels Patients receiving valproate and ethosuximide especially along with other anticonvulsants, should be monitored for alterations in serum concentrations of both drugs

Caution is recommended when DEPAKOTE (divalproex sodium) is administered with drugs affecting coagulation, e.g., aspirin and warfarin (See "Adverse Reactions" section)

*Carcinogenesis* Valproic acid was administered to Sprague Dawley rats and ICR (HA/ICR) mice at doses of 0, 80 and 170 mg/kg/day for two years Although a variety of neoplasms were observed in both species, the chief findings were a statistically significant increase in the incidence of subcutaneous fibrosarcomas in high dose male rats receiving valproic acid and a statistically significant dose related trend for benign pulmonary adenomas in male mice receiving valproic acid The significance of these findings for man is unknown at present

*Mutagenesis* Studies on valproic acid have been performed using bacterial and mammalian systems These studies have provided no evidence of a mutagenic potential for DEPAKOTE

*Fertility* Chronic toxicity studies in juvenile and adult rats and dogs demonstrated reduced spermatogenesis and testicular atrophy at doses greater than 200 mg/kg/day in rats and greater than 90 mg/kg/day in dogs Segment I fertility studies in rats have shown doses up to 350 mg/kg/day for 60 days to have no effect on fertility THE EFFECT OF DEPAKOTE (DIVALPROEX SODIUM) ON THE DEVELOPMENT OF THE TESTES AND ON SPERM PRODUCTION AND FERTILITY IN HUMANS IS UNKNOWN

*Pregnancy* Pregnancy Category D See "Warnings" section

*Nursing Mothers* Valproate is excreted in breast milk Concentrations in breast milk have been reported to be 1 10% of serum concentrations It is not known what effect this would have on a nursing infant Caution should be exercised when DEPAKOTE is administered to a nursing woman

**ADVERSE REACTIONS**: Since valproic acid and its derivatives have usually been used with other antiepileptic drugs, it is not possible in most cases, to determine whether the following adverse reactions can be ascribed to valproic acid alone or the combination of drugs

*Gastrointestinal* The most commonly reported side effects at the initiation of therapy are nausea, vomiting and indigestion These effects are usually transient and rarely require discontinuation of therapy Diarrhea, abdominal cramps and constipation have been reported Both anorexia with some weight loss and increased appetite with weight gain have also been reported The administration of enteric-coated divalproex sodium may result in reduction of gastrointestinal side effects in some patients[2]

*CNS Effects* Sedative effects have been noted in patients receiving valproic acid alone but are found most often in patients receiving combination therapy Sedation usually disappears upon reduction of other antiepileptic medication Tremor has been reported in patients receiving valproate and may be dose related Ataxia headache, nystagmus, diplopia, asterixis, "spots before eyes," dysarthria, dizziness, and incoordination have rarely been noted Rare cases of coma have been noted in patients receiving valproic acid alone or in conjunction with phenobarbital

*Dermatologic* Transient increases in hair loss have been observed Skin rash and erythema multiforme rarely have been noted

*Psychiatric* Emotional upset, depression, psychosis, aggression, hyperactivity and behavioral deterioration have been reported

*Musculoskeletal* Weakness has been reported

*Hematologic* Thrombocytopenia has been reported Valproic acid inhibits the secondary phase of platelet aggregation (See "Drug Interactions" section) This may be reflected in altered bleeding time Petechiae, bruising, hematoma formation, and frank hemorrhage have been reported (See "Precautions" section) Relative lymphocytosis and hypofibrinogenemia have been noted Leukopenia and eosinophilia have also been reported Anemia and bone marrow suppression have been reported

*Hepatic* Minor elevations of transaminases (e.g., SGOT and SGPT) and LDH are frequent and appear to be dose related Occasionally laboratory test results include, as well, increases in serum bilirubin and abnormal changes in other liver function tests These results may reflect potentially serious hepatotoxicity (See "Warnings" section)

*Endocrine* There have been reports of irregular menses and secondary amenorrhea and rare reports of breast enlargement and galactorrhea occurring in patients receiving valproic acid and its derivatives

Abnormal thyroid function tests have been reported (See "Precautions" section).

*Pancreatic* There have been reports of acute pancreatitis, including rare fatal cases, occurring in patients receiving valproic acid and its derivatives

*Metabolic* Hyperammonemia (See "Precautions" section)

Hyperglycinemia has been reported and has been associated with a fatal outcome in a patient with preexistent nonketotic hyperglycinemia

*Other* Edema of the extremities has been reported

**OVERDOSAGE**: Overdosage with valproic acid may result in deep coma

Since DEPAKOTE tablets are enteric-coated, the benefit of gastric lavage or emesis will vary with the time since ingestion General supportive measures should be applied with particular attention being given to the maintenance of adequate urinary output

Naloxone has been reported to reverse the CNS depressant effects of valproate overdosage Because naloxone could theoretically also reverse the antiepileptic effects of DEPAKOTE it should be used with caution

**DOSAGE AND ADMINISTRATION**: DEPAKOTE is administered orally The recommended initial dose is 15 mg/kg/day, increasing at one week intervals by 5 to 10 mg/kg/day until seizures are controlled or side effects preclude further increases The maximum recommended dosage is 60 mg/kg/day If the total daily dose exceeds 250 mg, it should be given in a divided regimen

*Conversion from DEPAKENE to DEPAKOTE* In patients previously receiving DEPAKENE (valproic acid) therapy, DEPAKOTE should be initiated at the same total daily dose and dosing schedule[3] After the patient is stabilized on DEPAKOTE a twice-a-day or three times-a-day schedule may be instituted in selected patients

The frequency of adverse effects (particularly elevated liver enzymes) may be dose-related The benefit of improved seizure control which may accompany higher doses should therefore be weighed against the possibility of a greater incidence of adverse reactions

A good correlation has not been established between daily dose, serum level and therapeutic effect However, therapeutic valproate serum levels for most patients will range from 50 to 100 mcg/ml Occasional patients may be controlled with serum levels lower or higher than this range

As the DEPAKOTE dosage is titrated upward, blood levels of phenobarbital and/or phenytoin may be affected (See "Precautions" section)

Patients who experience GI irritation may benefit from administration of the drug with food or by slowly building up the dose from an initial low level

**HOW SUPPLIED**: DEPAKOTE (divalproex sodium enteric coated tablets) are supplied as

125 mg salmon pink-colored tablets
Bottles of 100 (**NDC** 0074-6212-13)

250 mg peach-colored tablets
Bottles of 100 (**NDC** 0074-6214-13)
Abbo-Pac® unit dose packages of 100 (**NDC** 0074-6214-11)

500 mg lavender-colored tablets
Bottles of 100 (**NDC** 0074-6215-13)
Abbo-Pac® unit dose packages of 100 (**NDC** 0074-6215-11)

**REFERENCES**

1 Centers for Disease Control, Valproate A New Cause of Birth Defects — Report from Italy and Follow up from France, *Morbidity and Mortality Weekly Report* 32(33) 438-439, August 26, 1983
2 Wilder, B.J., et al, Gastrointestinal Tolerance of Divalproex Sodium, *Neurology* 33 808-811, June, 1983
3 Wilder, B.J., et al, Twice-Daily Dosing of Valproate with Divalproex *Clin Pharmacol Ther* 34(4) 501-504, 1983

Revised Jan , 1986

**Abbott Health Care Products, Inc.**
**North Chicago, IL60064**
7033813

# AMASOURCE

**Current information on AMA publications for physicians and patients**

**Health Policy Agenda for the American People** Over 425 representatives from 172 different health, health-related, business, government, and consumer groups met over the past five years to develop the *Health Policy Agenda for the American People*. Their mission: to examine immediate contemporary concerns, as well as issues expected to confront the health sector into the next decade and the next century. The *Health Policy Agenda* appears in three publications: the introductory *Summary Report;* the *Final Report,* in which health care issues, recommendations, and implementation plans are discussed in detail; and the *Reference Report,* containing background material developed during the project.

(OP-024) Summary Report . . . . . 12.00
(OP-025) Final Report . . . . 30.00
(OP-026) Reference Report . . . . . 50.00
(OP-027) Combination of OP-024 and OP-025 . . . . 35.00
(OP-023) 3-volume set . . 80.00

**Drug Evaluations Sixth Edition (DE6)** Contains comprehensive information about drugs, arranged by therapeutic use and class of drug. It compares and evaluates drugs as well as recommending drugs and regimens of choice. This new edition features more than 70 new drugs and 100 new investigational agents, a new chapter on drug therapy and expanded coverage on the immune system.
1800 pages (OP-255/6) . . . 75.00

**Guides to the Evaluation of Permanent Impairment** The world's best reference for evaluating the impaired. Each chapter of "Guides" explores a particular body system, and gives examples to assist you in your determination. Plus–this updated 2nd edition includes new tests, more clinical examples, the latest measurement techniques, more tables, greater depth, and a new chapter on sleep and arousal disorders.
454 pages (OP-254) 27.50

**AMA Health Insurance Claim Form** This is the standardized form required by the federal government and accepted by most insurers. Each order includes a free, detailed 12-page instruction booklet for proper completion of forms.

(OP-501) Single form, 1 page, 100 per pad, has Kodak bar code, ten pads/carton . . . . . 34.10
(OP-502) Snap-out form, 2-part NCR, has Kodak bar code, 1000/carton . . . . . 49.50
(OP-503) Continuous form, 2-part NCR with pinfeeds for computer printers, has Kodak bar code, 1000/carton . . . . . 51.75
(OP-505) Continuous form, 2-part NCR with pinfeeds for computer printers, has no Kodak bar code, 1000/carton 51.75

**Physicians' Resource Guide to Health Delivery Systems** There's nothing else like it. Contents of this unique and comprehensive publication include: history and overview of current systems; national resource listing of organizations and agencies involved with HMOs, PPOs, IPAs; glossary of terms; over 140 abstracts on 18 key topics.
122 pages (OP-157) . . . . 15.00

**Current Procedural Terminology 1987** Simplify claims processing with the five-digit code system provided in *Current Procedural Terminology (CPT).* Identifying more than 7,000 procedures and services, *CPT* is the most widely used procedure coding system in the U.S. *CPT* is employed by the Health Care Financing Administration as the basis for the HCPCS coding system, and is required for Medicare claims.
500 pages (OP-341/7) 30.00

**CPT 1987 floppy disk** is the medical procedures coding system of choice for physicians, third parties, and the federal government. CPT-1987 on floppy disk eliminates the time-consuming chore of entering all the procedures you perform into your data base or software. All procedure descriptions are presented in layman's terms, ideal for use with practice management and patient billing software.

Includes one copy of the CPT 1987 book and one copy of the data on the disk.
(OP-224) . . . . . 175.00

**For Credit Card Orders Call: 1-800/621-8335** Illinois Residents Call Collect: 312/645-4987

| OP Number | Quantity | Title/Description | Price Per Unit | Line Total |
|---|---|---|---|---|
| | | | $ | $ |
| | | | $ | $ |
| | | | $ | $ |
| | | | $ | $ |

*Please send your order and full payment to:*
**American Medical Association**
**P.O. Box 10946**
**Chicago, IL 60610-0946**

$10 minimum order. Costs include shipping and handling. Price is for 1-4 copies. For information and additional quantity costs, contact: Customer Service Department, American Medical Association, 535 N. Dearborn, Chicago, Illinois 60610 (312) 280-7168.

Subtotal $_____
AMA members (subtract 20%) $_____
ADD Sales Tax–Illinois & New York State Purchasers $_____
Foreign Orders Add $10 Per Unit $_____
Total Amount Due $_____

*Coupon expires December 31, 1987*
*Prices subject to change.*
*Please allow 4-6 weeks for delivery.*
*Orders are filled on the basis of product availability and date of receipt.*

Customer Name _____
(print clearly or type)
Company Name _____
Office/Department _____
Street Address _____
City/State/Zip (U.S.) _____
Foreign Country Name _____

☐ AMA Member ☐ Non-member
☐ Enclosed is my check made payable to the American Medical Association
☐ VISA ☐ MasterCard

Account #
Exp. Date __/__ Signature _____

WJM687

# The Western Journal of Medicine

SINCE 1902 ISSN 0093-0415

PO BOX 7602 • SAN FRANCISCO, CALIFORNIA 94120-7602 • TELEPHONE (415) 863-5522



MALCOLM S. M. WATTS, MD, *Editor*
LLOYD H. SMITH, Jr, MD, *Associate Editor*
DAVID GREER, *Managing Editor*

SALLY LINEBARGER, *Assistant Managing Editor*
SANDRA WILLETT, *Editorial Assistant*

JANICE ANDERSEN, *Copy Editor*
TERESA A. MORRISSEY, *Advertising Production Manager*
FRITZ C. HEATON, *Circulation Coordinator*

editorial communications to DR WATTS • business communications to MR GREER



Official Journal of the Arizona Medical Association, the California Medical Association, the Idaho Medical Association, the Montana Medical Association, the Nevada State Medical Association, the New Mexico Medical Society, the Utah State Medical Association, the Washington State Medical Association and the Wyoming Medical Society.

Affiliated Clinical Investigation Societies: the Western Association of Physicians; the Western Society for Clinical Investigation; the Western Section, American Federation for Clinical Research; the Western Society for Pediatric Research; the Western Region, Society for Investigative Dermatology.

Affiliated Specialty Society: California Society of Internal Medicine.



## EDITORIAL BOARD

*Chairman of the Board*
Malcolm S. M. Watts, San Francisco, Calif

*Associate Editor*
Lloyd H. Smith, Jr, San Francisco, Calif

*Editor for Clinical Investigation*
Kenneth D. Gardner, Jr, Albuquerque, NM

*Special Editor for Arizona*
Marshall B. Block, Phoenix, Ariz

*Special Editor for Idaho*
E. R. W. Fox, Coeur d'Alene, Idaho

*Special Editor for Montana*
Michael R. Oreskovich, Kalispell, Mont

*Special Editor for Nevada*
Owen C. Peck, Reno, Nev

*Special Editor for New Mexico*
I. Brian Taylor, Carlsbad, NM

*Special Editor for Utah*
John H. Holbrook, Salt Lake City, Utah

*Special Editor for Washington*
David Hopkins, Federal Way, Wash

*Special Editor for Wyoming*
Joseph P. Murphy, Casper, Wyo

*Allergy*
Harold S. Novey, Orange, Calif
Merle S. Scherr, Scottsdale, Ariz

*Anesthesiology*
Ronald D. Miller, San Francisco, Calif

*Cardiac and Thoracic Surgery*
Norman E. Shumway, Stanford, Calif

*Chest Diseases*
Leonard D. Hudson, Seattle, Wash
Thomas L. Petty, Denver, Colo

*Dermatology*
John H. Epstein, San Francisco, Calif
Clark Huff, Denver, Colo
Frank Parker, Portland, Dre
Gerald D. Weinstein, Irvine, Calif

*Emergency Medicine*
William A. Boehm, Alamogordo, NM
W. Richard Bukata, Van Nuys, Calif
Clark Chipman, Portland, Dre
Thomas Elmendorf, Davis, Calif

*General and Family Practice*
Harmon E. Holverson, Emmett, Idaho
Charles W. Huff, Casper, Wyo
Daniel D. Roberts, Central Point, Dre
J. Jerome Wildgen, Kalispell, Mont

*Internal Medicine*
Philip R. Alper, Burlingame, Calif
Robert W. Burroughs, Spokane, Wash
Theodore C. Eickhoff, Denver, Colo
Robert L. Hare, Portland, Dre
Harry R. Kimball, Boston, Mass
Robert H. Moser, Skokie, Ill
George A. Porter, Portland, Ore
Helen M. Ranney, San Diego, Calif
Laurens P. White, San Francisco, Calif
Ralph C. Williams, Jr, Albuquerque, NM

*Neurology*
J. Richard Baringer, Salt Lake City, Utah
Don F. Seelinger, Albuquerque, NM
W. C. Wiederholt, La Jolla, Calif

*Neurosurgery*
John R. Green, Phoenix, Ariz
George A. Djemann, Seattle, Wash
Charles B. Wilson, San Francisco, Calif

*Nuclear Medicine*
Joseph P. Kriss, Stanford, Calif

*Obstetrics and Gynecology*
Ralph W. Hale, Honolulu, Hawaii
W. LeRoy Heinrichs, Stanford, Calif
Morton A. Stenchever, Seattle, Wash

*Occupational Medicine*
Linda Hawes Clever, San Francisco, Calif

*Ophthalmology*
John L. Keltner, Davis, Calif
Bruce E. Spivey, San Francisco, Calif

*Orthopedics*
Ernest M. Burgess, Seattle, Wash
George E. Omer, Albuquerque, NM

*Otolaryngology*
Roger Boles, San Francisco, Calif
Paul H. Ward, Los Angeles, Calif

*Pathology*
Roy I. Davis, Phoenix, Ariz

*Pediatrics*
Allen W. Mathies, Jr, Pasadena, Calif
William D. Robertson, Seattle, Wash
Arnold L. Smith, Seattle, Wash

*Pharmacology*
Rubin Bressler, Tucson, Ariz

*Physical Medicine and Rehabilitation*
Robert G. Taylor, Sacramento, Calif

*Plastic Surgery*
Richard P. Jobe, Los Altos, Calif
Henry K. Kawamoto, Jr, Santa Monica, Calif

*Preventive Medicine and Public Health*
Joseph L. Lyon, Salt Lake City, Utah
Jonathan Mann, Geneva, Switz

*Psychiatry*
Ralph Crawshaw, Portland, Dre
Alan I. Levenson, Tucson, Ariz
R. Bruce Sloane, Los Angeles, Calif
Joe Paul Tupin, Sacramento, Calif

*Radiology*
M. Paul Capp, Tucson, Ariz
Albert A. Moss, Seattle, Wash
Marshall Rowen, Orange, Calif

*Surgery*
John Wesley Batdorf, Las Vegas, Nev
Daniel T. Cloud, Phoenix, Ariz
Paul A. Ebert, Chicago, Ill
Frank G. Moody, Houston, Tex

*Urology*
Richard Middleton, Salt Lake City, Utah
Thomas A. Stamey, Stanford, Calif

*Senior Members at Large*
Louis K. Diamond, San Francisco, Calif
Edgar Wayburn, San Francisco, Calif

## ADVISORY BOARD, CLINICAL INVESTIGATION

George D. Molnar, Univ of Alberta
Murray A. Katz, Univ of Arizona
Ross E. Petty, Univ of British Columbia
Eldon Shaffer, Univ of Calgary
M. Eric Gershwin, Univ of California, Davis
Jacob Katz, Univ of California, Irvine
Delbert A. Fisher, Univ of California, Los Angeles
Kenneth M. Moser, Univ of California, San Diego
H. Benfer Kaltreider, Univ of California, San Francisco
Alan S. Nies, Univ of Colorado
Irwin J. Schatz, Univ of Hawaii
John Peacock, Univ of Nevada
Sanford Schneider, Loma Linda Univ
Kenneth D. Gardner, Jr, Univ of New Mexico
J. David Bristow, Univ of Oregon
Robert M. McAllister, Univ of Southern California
R. Marvin Bala, Univ of Saskatchewan
Allen D. Cooper, Stanford Univ
Gerald Rothstein, Univ of Utah
David R. Saunders, Univ of Washington


## ADVERTISING INFORMATION

Advertising Sales Representatives

EAST: Saul G. Hornik, SGH, Inc, 12 Court Street, Freehold, NJ 07728 • (201) 972-1911/462-7422
MIDWEST: SGH, Inc, 100 South Wacker Drive, Suite 2030, Chicago, IL 60606 • (312) 782-1100
WEST: Lynne Jeffes, 1340 Paloma Avenue, Burlingame, CA 94010 • (415) 348-7478
CLASSIFIED: PO Box 7602, San Francisco, CA 94120-7602 • Tel: (415) 863-5522/863-6853

*Advertisements*—The journal is published the first week of the month. Advertising copy must be received no later than the first of the month preceding issue. Advertising rates will be sent on request. Acceptance of advertising is contingent upon approval by the Advertising Committee. *The journal reserves the right to reject any advertisement.*

## SUBSCRIPTION INFORMATION

The subscription price per year is $30 in the United States and Canada (US funds); $50 in all other countries. Single copies are $4.50 (which includes postage and handling). Address all subscription communications to:
THE WESTERN JOURNAL OF MEDICINE Circulation, PO Box 7602
San Francisco, CA 94120-7602 • Tel: (415) 863-5522, Ext 245

Allow six weeks for subscriptions to begin. Past issues must be bought individually. So long as reserve stocks are available, missing issue requests from subscribers are honored for up to six months after the issue date. Thereafter, the single copy rate of $4.50 is applicable for each issue available.

*Change of Address*—Requests for change of address should give both the old and new address. Allow six weeks for changeover.

## SUBMITTING MANUSCRIPTS

Manuscripts for consideration should be sent to the editor, Malcolm S. M. Watts, MD, PO Box 7602, San Francisco, CA 94120-7602.

*"Information for Authors"*—A complete guide to manuscript submission and *WJM* style appears in the January and July issues. Manuscripts may be prepared in accordance with the "Uniform Requirements for Manuscripts Submitted to Biomedical Journals" (*British Medical Journal*, June 12, 1982; *Annals of Internal Medicine*, June 1982).

*Author Responsibility*—Authors are responsible for all statements, conclusions and methods of presenting subjects. Articles are accepted on condition that they are contributed solely to this journal.

*Manuscripts*—Ordinarily manuscripts should not exceed 3,000 words (less than 15 typed double-spaced pages). The *original* manuscript and two copies should be submitted, typed double-spaced throughout. If photographic illustrations are desired, three sets of clear, unmounted black and white glossy prints should be supplied. For line drawings, original artwork or glossy prints are acceptable. Tables should be typed on separate sheets of paper.

*Clinical Investigation*—Papers that authors wish considered for the Clinical Investigation section should be so designated in the transmittal letter. Such papers should describe experimental work in humans that extensively and prospectively examines scientific hypotheses relating to disease.

## PUBLISHER


Copyright 1987 by the California Medical Association • Owned and Published by the California Medical Association.

All material subject to this copyright appearing in THE WESTERN JOURNAL OF MEDICINE may be photocopied for the noncommercial purpose of scientific or educational advancement. Volumes begin with January and July.



POLICY COMMITTEE
Frederick S. Armstrong
Laurens P. White
Richard F. Corlin
Charles W. Plows
Howard L. Lang
Roger K. Howe
Malcolm S. M. Watts


Second class postage paid at San Francisco and at additional mailing offices (USPS 084 480).

*Let Audio-Digest create time for you . . .*

# CONTINUING MEDICAL EDUCATION ON AUDIO CASSETTES

***Send for FREE "No Obligation" Hour Program*** *We want you to hear for yourself how Audio-Digest can create time for you—and why it is a completely interactive system of postgraduate medical education that provides . . .*

- ***Editorial Excellence.*** *Our Editorial Staff deletes irrelevant trivia, to give you only the 'meat' of the meetings and smooth, clear and concise delivery of clinical information.*
- ***Valuable Printed Reference Materials.*** *Each one-hour program is accompanied by detailed outline summaries, graphs, charts, bibliographies, supplemental reading references—including the availability of self-assessment/accreditation tests (which we computer score, at no added cost).*
- ***Category I Approved.*** *Each one-hour Audio-Digest program is eligible for two Category I credit hours towards the American Medical Association's Physician's Recognition Award, as well as being approved by other specialty organizations.*
- ***Our Guarantee.*** *If at any time you feel Audio-Digest isn't a most beneficial source of continuing medical education—you're free to cancel. (We'd want you to, and we'd want to know how we failed you). You'll receive a complete, and prompt refund for the balance of the subscription.*

***DETACH AND MAIL***

***Check FREE Specialty Program Desired***

- ☐ ***Anesthesiology***
- ☐ ***Emergency Medicine***
- ☐ ***Family Practice***
- ☐ ***Gastroenterology****
- ☐ ***Internal Medicine***
- ☐ ***Obstetrics/Gynecology***
- ☐ ***Ophthalmology***
- ☐ ***Otolaryngology—Head and Neck Surgery***
- ☐ ***Orthopaedics****
- ☐ ***Pediatrics***
- ☐ ***Psychiatry***
- ☐ ***Surgery***
- ☐ ***Urology****

☐ ***Yes!*** *Please send me the FREE specialty program I've checked above. I understand this program is accompanied by valuable printed reference materials and subscription ordering information.*

☐ ***I'm sold!*** *Rush me my FREE program and enter my subscription. Enclosed is my check for $86.33—special INTRODUCTORY RATE, 7 months, 14 issues. *Gastroenterology, *Orthopaedics, *Urology—$43.16, 7 months, 7 issues.*

_____
*Name (please print)*

_____
*Address*

_____ _____ _____
*City* *State* *Zip Code*

( ) _____
*Telephone*

***Audio-Digest*** *Foundation®*
*A Non-Profit Subsidiary of the California Medical Association*
*1577 East Chevy Chase Drive*
*Glendale, CA 91206*

***CALL TOLL FREE 1-800/423-2308***
***1-800/232-2165*** *(CA)*

6674

# The Only Microencapsulated KCl Delivery System That Delivers Both 8mEq K & 10mEq K

## MICRO·K®
(Potassium Chloride)
*Controlled-Release Extencaps® 600 mg (8 mEq K)*

## MICRO·K® 10
(Potassium Chloride)
*Controlled-Release Extencaps® 750 mg (10 mEq K)*

A·H·ROBINS

Pharmaceutical Division, Richmond, Virginia 23261-6609
Member of Certified Medical Representatives Institute

©A.H. Robins Company 1986

The Western Journal of Medicine

VOLUME 146 • NUMBER 6 • JUNE 1987

# CONTENTS

THE FRANCIS A. COUNTWAY
LIBRARY OF MEDICINE
BOSTON, MA

JUN 19 1987

## CLINICAL INVESTIGATION

695 **Clorazepate Use May Prevent Alcohol Withdrawal Convulsions**

VICTOR G. HADDOX, MD, JD; T. GEORGE BIDDER, MD; LESTER E. WALDRON; PATRICIA DERBY and SUSAN M. W. ACHEN, MPH, RN

*From the Alcohol Treatment Unit, the Department of Psychopharmacology, the Department of General Medicine and the Research Service, Veterans Administration Medical Center, Sepulveda; the Department of Psychiatry, University of California, Los Angeles, School of Medicine, and the Valley Presbyterian Hospital Olmstead Memorial, Van Nuys, California.*

## CLINICAL MEDICINE

697 **Increased Use of Medical Services and Antibiotics by Children Who Claim a Prior Penicillin Sensitivity**

MICHAEL J. KRAEMER, MD; HOPE CAPRYE-BOOS, MD, ARNP, and HENRY S. BERMAN, MD

*From the Spokane Allergy and Asthma Clinic, the Intercollegiate Center for Nursing Education and the Group Health of Spokane, Spokane, Washington.*

701 **Treatment of Severe Hypertension and Hypertensive Crises With Nifedipine**

MARK C. HOUSTON, MD

*From the Division of General Internal Medicine, Medical Intensive Care Unit, Cooperative Care Center, Vanderbilt University Medical Center, Nashville, Tennessee.*

## MEDICAL PROGRESS

705 **Treatable Dementias**

MICHAEL E. MAHLER, MD; JEFFREY L. CUMMINGS, MD, and D. FRANK BENSON, MD

*From the Department of Neurology, Reed Neurological Research Center, University of California, Los Angeles, School of Medicine, and the Neurobehavior Unit, Veterans Administration Medical Center (Brentwood Division), Los Angeles.*

## SPECIALTY CONFERENCE

713 **Cardiac Ischemia. Part I—Metabolic and Physiologic Responses**

Moderator: GLENN A. LANGER, MD

Discussants: JAMES N. WEISS, MD, and HEINRICH R. SCHELBERT, PhD

*An edited summary of an Interdepartmental Conference arranged by the Department of Medicine of the UCLA School of Medicine, Los Angeles. The Director of Conferences is William M. Partridge, MD, Professor of Medicine.*

## MEDICAL STAFF CONFERENCE

724 **Peptic Ulcer Disease—Pathophysiology and Current Medical Management**

Discussant: BRUCE F. SCHARSCHMIDT, MD

*A discussion selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco, School of Medicine. Taken from a transcription, it was prepared by Drs Homer A. Boushey, Associate Professor of Medicine, and David G. Warnock, Associate Professor of Medicine, under the direction of Dr Lloyd H. Smith, Jr, Professor of Medicine and Associate Dean in the School of Medicine.*

*(Continued on Page 671)*

*In mild-to-moderate hypertension†*

# CAPOTEN (captopril tablets)

# THERE'S SAFETY IN OUR NUMBERS

**• 8 years in clinical use**
CAPOTEN has an established record of practical clinical usage, spanning nearly a decade.

**• 16 million prescriptions**
Since its successful introduction in the U.S., CAPOTEN has earned the prescribing confidence of physicians.[1]

**• 5 million patients**
CAPOTEN has provided well-tolerated therapy for over 5 million patients worldwide.

**• 3,000 clinical papers**
More than 3,000 informative articles have been published about CAPOTEN.

## Convenient, well-tolerated therapy that promotes patient compliance

Comparison of Adverse Effects for CAPOTEN (≤ 100 mg) versus Placebo in Hypertensive Patients with Normal Renal Function (N = 1,622)‡[2]

| ADVERSE EFFECT | CAPOTEN (N = 1,174) (% affected) | Placebo (N = 448) (% affected) |
|---|---|---|
| Headache | 5.2 | 6.9 |
| Rash | 3.7 | 2.5 |
| Dizziness | 3.5 | 2.0 |
| Nausea | 3.2 | 2.0 |
| Fatigue | 3.1 | 2.0 |
| Taste alteration | 1.5 | 1.1 |
| Gastrointestinal | 1.4 | 0.7 |
| Diarrhea | 1.1 | 1.1 |

‡None of the differences between captopril and placebo was statistically significant. For the most part, adverse effects were mild and transient and usually did not require discontinuation of therapy. Only 5.5% of the patients in this data base discontinued because of an adverse effect. Data include adverse effects for CAPOTEN with an incidence greater than 1%.

†CAPOTEN may be used as initial therapy only for patients with normal renal function in whom the risk of neutropenia/agranulocytosis is relatively low (1 out of over 8,600 in clinical trials). Use special precautions in patients with impaired renal function, collagen vascular disorders, or those exposed to other drugs known to affect the white cells or immune response. Evaluation of hypertensives should always include assessment of renal function. See INDICATIONS AND USAGE, WARNINGS, and ADVERSE REACTIONS in the brief summary on the adjacent page.

*ACE* INHIBITOR*

**CAPOTEN® captopril tablets** **LOW DOSE**

*FIRST-LINE THERAPY THAT PUTS QUALITY OF LIFE FIRST*

*Angiotensin Converting Enzyme

SQUIBB

**CAPOTEN® TABLETS**
**Captopril Tablets**

**INDICATIONS: Hypertension** – CAPOTEN (captopril) is indicated for the treatment of hypertension. Consideration should be given to the risk of neutropenia/agranulocytosis (see WARNINGS). CAPOTEN may be used as initial therapy for patients with normal renal function, in whom the risk is relatively low. In patients with impaired renal function, particularly those with collagen vascular disease, captopril should be reserved for those who have either developed unacceptable side effects on other drugs, or have failed to respond satisfactorily to drug combinations. CAPOTEN is effective alone and in combination with other antihypertensive agents, especially thiazide-type diuretics.

**Heart Failure:** CAPOTEN (captopril) is indicated in patients with heart failure who have not responded adequately to or cannot be controlled by conventional diuretic and digitalis therapy. CAPOTEN is to be used with diuretics and digitalis.

**WARNINGS: Neutropenia/Agranulocytosis** – Neutropenia (< 1000/mm³) with myeloid hypoplasia has resulted from use of captopril. About half of the neutropenic patients developed systemic or oral cavity infections or other features of the syndrome of agranulocytosis. The risk of neutropenia is dependent on the clinical status of the patient:

In clinical trials in patients with hypertension who have normal renal function (serum creatinine <1.6 mg/dL and no collagen vascular disease), neutropenia has been seen in one patient out of over 8,600 exposed. In patients with some degree of renal failure (serum creatinine at least 1.6 mg/dL) but no collagen vascular disease, the risk in clinical trials was about 1 per 500. Doses were relatively high in these patients, particularly in view of their diminished renal function. In patients with collagen vascular diseases (e.g., systemic lupus erythematosus, scleroderma) and impaired renal function, neutropenia occurred in 3.7% of patients in clinical trials. While none of the over 750 patients in formal clinical trials of heart failure developed neutropenia, it has occurred during subsequent clinical experience. Of reported cases, about half had serum creatinine ≥ 1.6 mg/dL and more than 75% received procainamide. In heart failure, it appears that the same risk factors for neutropenia are present.

Neutropenia has appeared usually within 3 months after starting therapy, associated with myeloid hypoplasia and frequently accompanied by erythroid hypoplasia and decreased numbers of megakaryocytes (e.g., hypoplastic bone marrow and pancytopenia); anemia and thrombocytopenia were sometimes seen. Neutrophils generally returned to normal in about 2 weeks after captopril was discontinued, and serious infections were limited to clinically complex patients. About 13% of the cases of neutropenia have ended fatally, but almost all fatalities were in patients with serious illness, having collagen vascular disease, renal failure, heart failure or immunosuppressant therapy, or a combination of these complicating factors.

**Evaluation of the hypertensive or heart failure patient should always include assessment of renal function.** If captopril is used in patients with impaired renal function, white blood cell and differential counts should be evaluated prior to starting treatment and at approximately 2-week intervals for about 3 months, then periodically. In patients with collagen vascular disease or who are exposed to other drugs known to affect the white cells or immune response, particularly when there is impaired renal function, captopril should be used only after an assessment of benefit and risk, and then with caution. All patients treated with captopril should be told to report any signs of infection (e.g., sore throat, fever); if infection is suspected, perform counts without delay. Since discontinuation of captopril and other drugs has generally led to prompt return of the white count to normal, upon confirmation of neutropenia (neutrophil count < 1000/mm³) withdraw captopril and closely follow the patient's course.

**Proteinuria** – Total urinary proteins >1 g/day were seen in about 0.7% of patients on captopril. About 90% of affected patients had evidence of prior renal disease or received high doses (>150 mg/day), or both. The nephrotic syndrome occurred in about one-fifth of proteinuric patients. In most cases, proteinuria subsided or cleared within 6 months whether or not captopril was continued. The BUN and creatinine were seldom altered in proteinuric patients. Since most cases of proteinuria occurred by the 8th month of therapy, patients with prior renal disease or those receiving captopril at doses >150 mg/day should have urinary protein estimates (dip-stick on 1st morning urine) before therapy, and periodically thereafter.

**Hypotension** – Excessive hypotension was rarely seen in hypertensive patients but is a possibility in severely salt/volume-depleted persons such as those treated vigorously with diuretics (see PRECAUTIONS [Drug Interactions]).

In heart failure, where blood pressure was either normal or low, transient decreases in mean blood pressure >20% were recorded in about half of the patients. This transient hypotension may occur after any of the first several doses and is usually well tolerated, although rarely it has been associated with arrhythmia or conduction defects. A starting dose of 6.25 or 12.5 mg tid may minimize the hypotensive effect. Patients should be followed closely for the first 2 weeks of treatment and whenever the dose of captopril and/or diuretic is increased.

**BECAUSE OF THE POTENTIAL FALL IN BLOOD PRESSURE IN THESE PATIENTS, THERAPY SHOULD BE STARTED UNDER VERY CLOSE MEDICAL SUPERVISION.**

**PRECAUTIONS: General:** *Impaired Renal Function,* Hypertension – Some hypertensive patients with renal disease, particularly those with severe renal artery stenosis, have developed increases in BUN and serum creatinine. It may be necessary to reduce captopril dosage and/or discontinue diuretic. For some of these patients, normalization of blood pressure and maintenance of adequate renal perfusion may not be possible. Heart Failure – About 20% of patients develop stable elevations of BUN and serum creatinine >20% above normal or baseline upon long-term treatment. Less than 5% of patients, generally with severe preexisting renal disease, required discontinuation due to progressively increasing creatinine. See DOSAGE AND ADMINISTRATION, ADVERSE REACTIONS [Altered Laboratory Findings]. *Valvular Stenosis* – A theoretical concern, for risk of decreased coronary perfusion, has been noted regarding vasodilator treatment in patients with aortic stenosis due to decreased afterload reduction.

*Surgery/Anesthesia* – If hypotension occurs during major surgery or anesthesia, and is considered due to the effects of captopril, it is correctable by volume expansion.

**Drug Interactions:** *Hypotension: Patients on Diuretic Therapy* – Precipitous redu tion of blood pressure may occasionally occur within the 1st hour after administratic of the initial captopril dose in patients on diuretics, especially those recently placed c diuretics, and those on severe dietary salt restriction or dialysis. This possibility c be minimized by either discontinuing the diuretic or increasing the salt intake abo 1 week prior to initiation of captopril therapy or by initiating therapy with sm doses (6.25 or 12.5 mg). Alternatively, provide medical supervision for at least 1 ho after the initial dose.

*Agents Having Vasodilator Activity* – In heart failure patients, vasodilators shou be administered with caution.

*Agents Causing Renin Release* – Captopril's effect will be augmented by antihypertensi agents that cause renin release.

*Agents Affecting Sympathetic Activity* – The sympathetic nervous system may especially important in supporting blood pressure in patients receiving captop alone or with diuretics. Beta-adrenergic blocking drugs add some further antihypertens effect to captopril, but the overall response is less than additive. Therefore, use ager affecting sympathetic activity (e.g., ganglionic blocking agents or adrenergic neur blocking agents) with caution.

*Agents Increasing Serum Potassium* – Give potassium-sparing diuretics or potassiu supplements only for documented hypokalemia, and then with caution, since th may lead to a significant increase of serum potassium. Use potassium-containing s substitutes with caution.

*Inhibitors of Endogenous Prostaglandin Synthesis* – Indomethacin and other nonsteroi anti-inflammatory agents may reduce the antihypertensive effect of captopril, es cially in low renin hypertension.

**Drug/Laboratory Test Interaction:** Captopril may cause a false-positive ur test for acetone.

**Carcinogenesis, Mutagenesis and Impairment of Fertility:** Two-year stud with doses of 50 to 1350 mg/kg/day in mice and rats failed to show any evidence carcinogenic potential. Studies in rats have revealed no impairment of fertility.

**Pregnancy: Category C** – There are no adequate and well-controlled studies pregnant women. Embryocidal effects and craniofacial malformations were obser in rabbits. Therefore, captopril should be used during pregnancy, or for patie likely to become pregnant, only if the potential benefit outweighs the potential risk the fetus. Captopril crosses the human placenta.

**Nursing Mothers:** Captopril is secreted in human milk. Exercise caution when ministering captopril to a nursing woman, and, in general, nursing should be interrup

**Pediatric Use:** Safety and effectiveness in children have not been establis although there is limited experience with use of captopril in children from 2 mon to 15 years of age. Dosage, on a weight basis, was comparable to that used in ad Captopril should be used in children only if other measures for controlling blo pressure have not been effective.

**ADVERSE REACTIONS:** Reported incidences are based on clinical trials inv ing approximately 7000 patients.

*Renal* – About 1 of 100 patients developed proteinuria (see WARNINGS). Rena sufficiency, renal failure, polyuria, oliguria, and urinary frequency in 1 to 2 of 1000 patie

*Hematologic* – Neutropenia/agranulocytosis have occurred (see WARNINGS). A mia, thrombocytopenia, and pancytopenia have been reported.

*Dermatologic* – Rash (usually maculopapular, rarely urticarial), often with prur and sometimes with fever and eosinophilia, in about 4 to 7 of 100 patients (depend on renal status and dose), usually during the 1st 4 weeks of therapy. Pruritus, with rash, in about 2 of 100 patients. A reversible associated pemphigoid-like lesion, photosensitivity have also been reported. Angioedema of the face, mucous m branes of the mouth, or of the extremities in about 1 of 1000 patients – reversible discontinuance of captopril therapy. One case of laryngeal edema reported. Flush or pallor in 2 to 5 of 1000 patients.

*Cardiovascular* – Hypotension may occur, see WARNINGS and PRECAUTIONS (Drug Interactions) for discussion of hypotension on initiation of captopril ther Tachycardia, chest pain, and palpitations each in about 1 of 100 patients. An pectoris, myocardial infarction, Raynaud's syndrome, and congestive heart fai each in 2 to 3 of 1000 patients.

*Dysgeusia* – About 2 to 4 (depending on renal status and dose) of 100 pati developed a diminution or loss of taste perception; taste impairment is reversible usually self-limited even with continued drug use (2 to 3 months). Gastric irrita abdominal pain, nausea, vomiting, diarrhea, anorexia, constipation, aphthous ul peptic ulcer, dizziness, headache, malaise, fatigue, insomnia, dry mouth, dysp cough, alopecia, and paresthesias reported in about 0.5 to 2% of patients but did appear at increased frequency compared to placebo or other treatments use controlled trials.

**Altered Laboratory Findings:** Elevations of liver enzymes in a few pati although no causal relationship has been established. Rarely cholestatic jaundice hepatocellular injury with or without secondary cholestasis, have been reporte transient elevation of BUN and serum creatinine may occur, especially in volu depleted or renovascular hypertensive patients. In instances of rapid reductio longstanding or severely elevated blood pressure, the glomerular filtration rate decrease transiently, also resulting in transient rises in serum creatinine and B Small increases in serum potassium concentration frequently occur, especial patients with renal impairment (see PRECAUTIONS).

**OVERDOSAGE:** Primary concern is correction of hypotension. Volume expan with an I.V. infusion of normal saline is the treatment of choice for restoratio blood pressure. Captopril may be removed from the general circulation by hemodia

**DOSAGE AND ADMINISTRATION:** CAPOTEN (captopril) should be t one hour before meals. In hypertension, CAPOTEN may be dosed bid or tid. Do must be individualized; see DOSAGE AND ADMINISTRATION section of p age insert for detailed information regarding dosage in hypertension and in rt failure. Because CAPOTEN (captopril) is excreted primarily by the kidneys, do adjustments are recommended for patients with impaired renal function.

**Consult package insert before prescribing CAPOTEN (captopril).**

**HOW SUPPLIED:** Available in tablets of 12.5, 25, 50, and 100 mg in bottles c (25 mg also available in bottles of 1000), and in UNIMATIC® single dose packs c tablets. (J3-6 D

References:
1. PDS Alpha, *National Prescription Report,* Pharmaceutical Data Services, Subsidiary of McKesson Corporation.
2. Data on file, Squibb Institute for Medical Research.

SQUIBB

*INNOVATORS IN CARDIOVASCULAR MEDICI*

©1987 E. R. Squibb & Sons, Inc., Princeton, NJ 527-555 Issued: January 1987

The Western Journal of Medicine

# CONTENTS

(Continued from Page 667)

## EPITOMES—IMPORTANT ADVANCES IN CLINICAL MEDICINE


### General Surgery

*Items of progress in general surgery. Each item in the judgment of a panel of knowledgeable physicians has recently become reasonably firmly established, both as to scientific fact and important clinical significance.*

734 **New Advances in Pancreatic Transplantation**
PATRICK SOON-SHIONG, MD, and GEOFFREY WHITE, MD

734 **Alternatives to Total Mastectomy for Carcinoma of the Breast**
ARMANDO GIULIANO, MD

735 **Treatment of Renovascular Hypertension**
FRED A. WEAVER, MD

736 **Anal-Sphincter Saving Operations**
ERIC W. FONKALSRUD, MD

737 **Treatment of Asymptomatic Gallstones**
RICHARD A. CRASS, MD

737 **Fine-Needle Aspiration of Thyroid Nodules**
EUGENE A. WOLTERING, MD

738 **Heart and Heart-Lung Transplantation**
VAUGHN A. STARNES, MD, and NORMAN E. SHUMWAY, MD

738 **Brain Death**
A. CRAIG EDDY, MD, and CHARLES L. RICE, MD


## EDITORIALS


740 **Contemporary Aims for American Medicine**

740 **Differentiating Treatable Causes of Dementia**
LEON J. EPSTEIN, MD, PhD
*From the Langley Porter Psychiatric Institute, University of California, San Francisco, School of Medicine.*


## CASE REPORTS


742 **Reversible Renal Resistance to Aldosterone Associated With Interstitial Nephritis**
JOHN J. REGAN, Jr, MD; CHARLES S. GREENBERG, MD; ARSHAG D. MOORADIAN, MD; NANCY STALEY, MD, and FRANK Q. NUTTALL, MD, PhD
*From the Section of Endocrinology, Veterans Administration Medical Center, and the Departments of Medicine and Pathology, University of Minnesota Medical School, Minneapolis.*

745 **Sarcoidosis and Pheochromocytoma**
KEVIN M. MURRAY, MD, and RICHARD F. SCHILLACI, MD
*From the Department of Internal Medicine (Pulmonary Division) and the Clinical Investigation Department, Naval Hospital, San Diego.*


## CORRESPONDENCE


748 **Management of Lumbar Disc Disease**
MICHAEL H. SUKOFF, MD

748 **Infection Associated With Joystick Mimicking a Spider Bite**
GARWIN B. SOE, MD; LARRY M. GERSTEN, MD; JEANETTE WILKINS, MD; MICHAEL J. PATZAKIS, MD, and J. PAUL HARVEY, MD

748 **The Elusiveness of Truth**
LAURENS P. WHITE, MD

749 **Wright's Law**
E. S. WRIGHT, MD

749 **Dollar Mentality**
HOWARD F. LONG, MD, MPH

749 **Cultural Change, Social Disintegration and Medicine**
EUGENE E. BLECK, MD

750 **Importance of Dive Tables in Scuba Diving**
SUSAN EILE


(Continued on Page 672)

(Continued from Page 671)

## TOPICS IN PRIMARY CARE MEDICINE

751 **A Clinician's Guide to Helping Patients Change Behavior**

ALBERT R. MARTIN, MD, and THOMAS J. COATES, PhD

*From the Division of General Internal Medicine, Department of Medicine, University of California, San Francisco, School of Medicine.*

## FORUM

754 **Contemporary Aims for American Medicine—1987—A Report on a Forum**

MALCOLM S. M. WATTS, MD

## COMMENTARY

759 **Fear of the Unknown**

E. R. W. FOX, MD

*Dr Fox is in private practice in Coeur d'Alene and is the Special Editor for Idaho.*

## INFORMATION

761 **Use and Safety of Antimicrobial Agents During Pregnancy**

ANTHONY W. CHOW, MD, FRCP(C), and PETER J. JEWESSON, PhD(Pharm)

*From the Division of Infectious Diseases, Department of Medicine, and the Division of Clinical Pharmacy, Department of Pharmacy, G. F. Strong Rehabilitation Center, Vancouver General Hospital, University of British Columbia Faculty of Medicine, Vancouver.*

765 **Leaving a Cardiology Service Against Medical Advice—A Follow-Up Study**

HERBERT N. OCHITILL, MD; RANDOLPH C. BYRD, MD, and JANET GREENE

*From the Division of Cardiology and the Department of Psychiatry, San Francisco General Hospital Medical Center and the University of California, San Francisco, School of Medicine.*

## OTHER FEATURES

681 **Subscription Information**

688 **Continuing Medical Education Activities in Arizona; California, Hawaii and Nevada; Idaho; Montana; New Mexico; Utah; Washington; Wyoming**

766 **Volume Index**

778 **Classified Advertising**

780 **In Memoriam**

793 **Wyoming Medical Society Annual Meeting**

801 **Idaho Medical Association Annual Meeting**

806 **Western State Medical Associations' Meetings**

★ **Official Journal of the Arizona Medical Association, the California Medical Association, the Idaho Medical Association, the Montana Medical Association, the Nevada State Medical Association, the New Mexico Medical Society, the Utah State Medical Association, the Washington State Medical Association and the Wyoming Medical Society. Affiliated Specialty Society: California Society of Internal Medicine.**

★ **Affiliated Clinical Investigation Societies: the Western Association of Physicians; the Western Society for Clinical Investigation; the Western Section, American Federation for Clinical Research; the Western Society for Pediatric Research; the Western Region, Society for Investigative Dermatology.**

## chnology

IE RESIDENT" is a compre-
nsive medical office computer
em designed to meet the
nplex needs of today's
dical office.

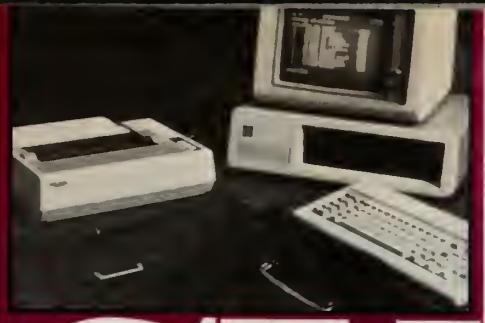
programs in "THE RESIDENT"
accessed through menus.
erations are smooth and
y. Patient record access can
by name, partial name, or
ce-defined code. Mainten-
e tables (RVS, ICD-9, Insur-
e Company, etc.) may be set
using existing codes com-
n to the particular office.

rations may be temporarily
ended, a new task per-
ned, and then resume the
inal task at the exact place
re operation was sus-
ded. This feature is useful
adding a new insurance
pany without having to skip
ugh numerous screens.

software was designed for
p practices, but performs
lly as well in a busy solo
tice.

## pport Service

over 7 years, SYZYGY has
ided such services as: com-
r installations, cabling,
training, management con-
ng, and hardware/software
port.



# SYZYGY

## Key Features

- *Latest industry-accepted software technology*
- *Protection against software obsolescence*
- *Modular software application packages*
- *Multi-user/multi-terminals/multi-office*
- *Three tiered self-help capability*
- *Office defined practice policies*
- *No codes to remember*
- *Suspend an operation, jump to a new task, and return*
- *Bridge between database and word processor*

## Modular Software

With Wallaby's modular software, there is never a need to purchase and implement more capability than you need. You buy only what you require. Each software configuration, however, is complete of itself...there are no costly options to any module to fill the needs of a particular medical speciality. For example:

- *Patient Billing*
- *Accounts Receivable*
- *Practice Analysis*
- *Insurance Forms Formatter*
- *Appointment Scheduling*
- *Report Generator*
- *Electronic Forms Submission*
- *Word Processing*
- *General Ledger*
- *Accounts Payable*
- *Payroll*
- *Supply Inventory*
- *Telecommunications*

## Expandability

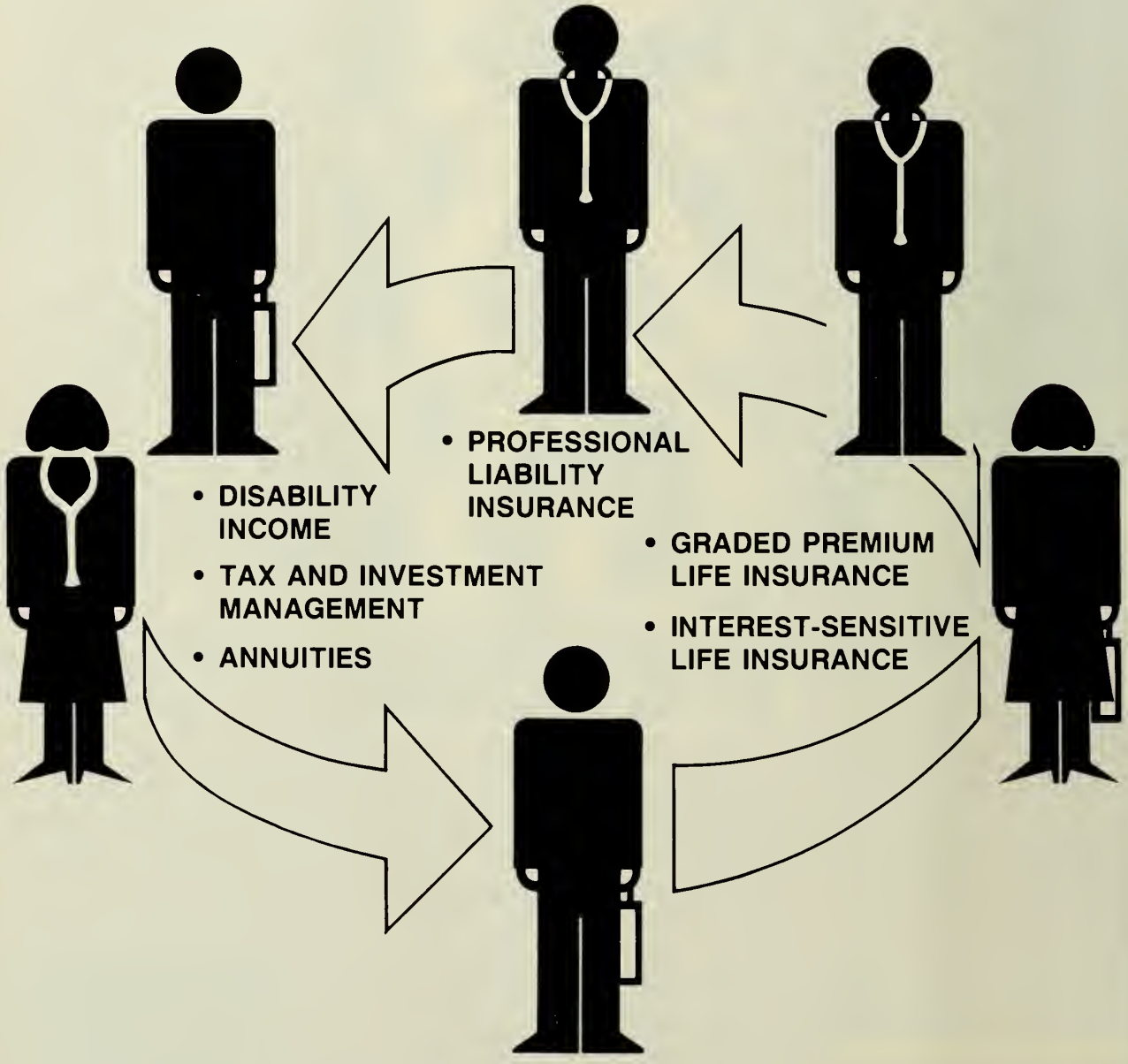
Expansion can take place at any time...the user may add terminals and printers, increase the storage capacity, and install additional software modules without modification of existing operational procedures. This Medical Practice Management System grows to match your needs.

Y Z Y G Y®
mputer Systems, Inc.
Borrego Court, San Dimas, CA 91773

*FOR MORE INFORMATION PLEASE CALL*

(800) 824-0532
(818) 332-3320

# ONE-STOP FINANCIAL CENTER

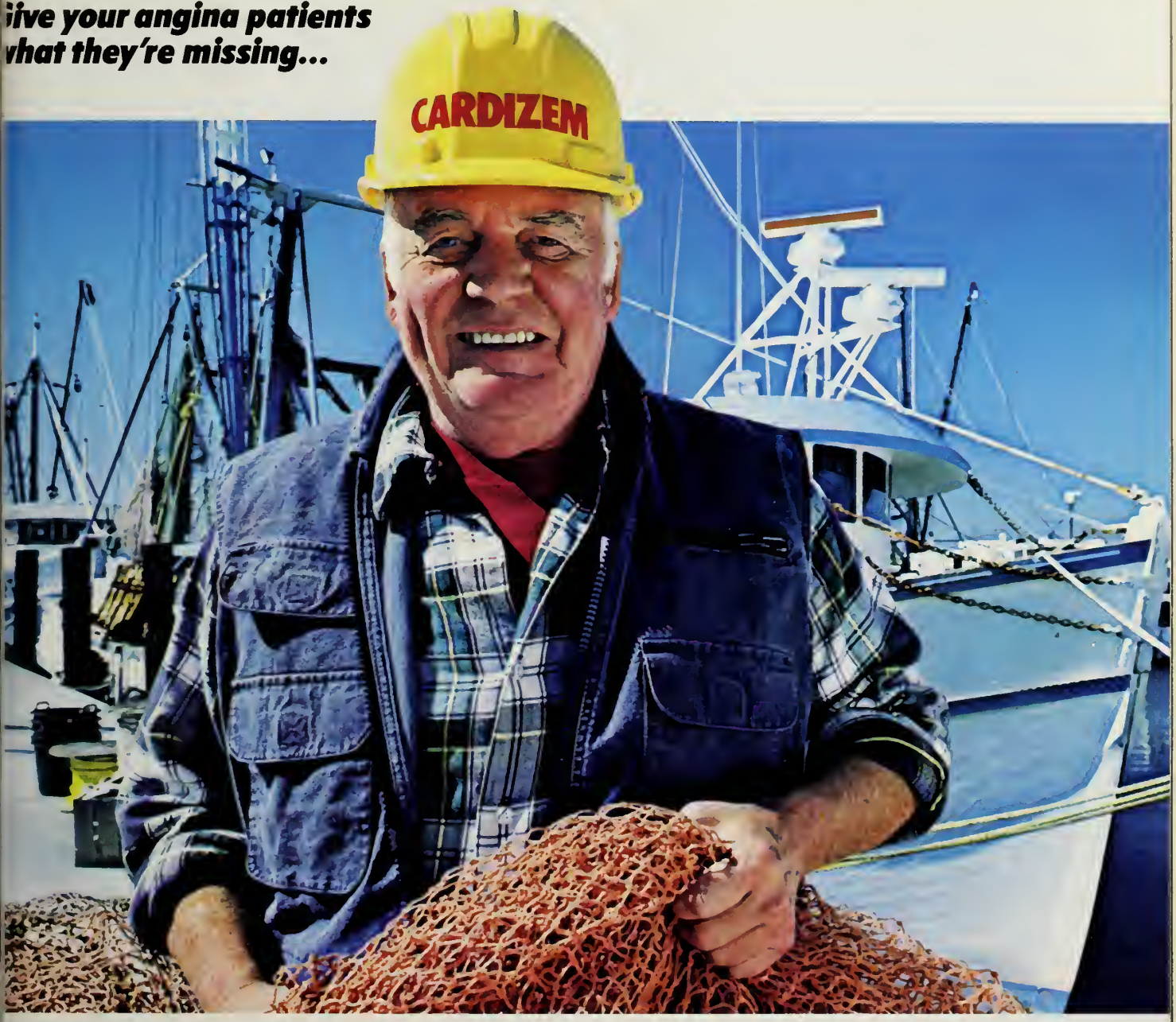



Choose the professionals. Through our subsidiary, The Doctors' Company Insurance Services, we offer physicians the convenience of a comprehensive source for income protection and financial planning services.

**THE DOCTORS' COMPANY**

401 WILSHIRE BOULEVARD, SANTA MONICA, CA 90401
(213) 451-3011 (800) 352-7271 (CALIFORNIA) (800) 421-2368 (OUTSIDE CALIFORNIA)

*ive your angina patients*
*vhat they're missing...*




# CARDIZEM®: FEW SIDE EFFECTS

diltiazem HCl/Marion

- **Antianginal action includes dilatation of coronary arteries, a decrease in vascular resistance/afterload, and a reduction in heart rate**
- **Proven efficacy when used alone in angina[1]**
- **Compatible with other antianginals[2,3]***
- **A safe choice for angina patients with coexisting hypertension, asthma, COPD, or PVD[4,5]**

90 mg NEW 120 mg GREATER DOSAGE FLEXIBILITY

***See Warnings and Precautions.**

*Please see brief summary of prescribing information on the next page.*

# CARDIZEM® diltiazem HCl/Marion

# FEW SIDE EFFECTS IN ANTIANGINAL THERAPY

## 60 mg tid or qid

***Brief Summary***
*Professional Use Information*

***CARDIZEM®***
*(diltiazem HCl) 30 mg and 60 mg Tablets*

***CONTRAINDICATIONS***
*CARDIZEM is contraindicated in (1) patients with sick sinus syndrome except in the presence of a functioning ventricular pacemaker, (2) patients with second- or third-degree AV block except in the presence of a functioning ventricular pacemaker, and (3) patients with hypotension (less than 90 mm Hg systolic).*

***WARNINGS***

1. ***Cardiac Conduction.*** *CARDIZEM prolongs AV node refractory periods without significantly prolonging sinus node recovery time, except in patients with sick sinus syndrome. This effect may rarely result in abnormally slow heart rates (particularly in patients with sick sinus syndrome) or second- or third-degree AV block (six of 1,243 patients for 0.48%). Concomitant use of diltiazem with beta-blockers or digitalis may result in additive effects on cardiac conduction. A patient with Prinzmetal's angina developed periods of asystole (2 to 5 seconds) after a single dose of 60 mg of diltiazem.*
2. ***Congestive Heart Failure.*** *Although diltiazem has a negative inotropic effect in isolated animal tissue preparations, hemodynamic studies in humans with normal ventricular function have not shown a reduction in cardiac index nor consistent negative effects on contractility (dp/dt).*
   *Experience with the use of CARDIZEM alone or in combination with beta-blockers in patients with impaired ventricular function is very limited. Caution should be exercised when using the drug in such patients.*
3. ***Hypotension.*** *Decreases in blood pressure associated with CARDIZEM therapy may occasionally result in symptomatic hypotension.*
4. ***Acute Hepatic Injury.*** *In rare instances, significant elevations in enzymes such as alkaline phosphatase, CPK, LDH, SGOT, SGPT, and other symptoms consistent with acute hepatic injury have been noted. These reactions have been reversible upon discontinuation of drug therapy. The relationship to CARDIZEM is uncertain in most cases, but probable in some. (See PRECAUTIONS.)*

***PRECAUTIONS***
***General.*** *CARDIZEM (diltiazem hydrochloride) is extensively metabolized by the liver and excreted by the kidneys and in bile. As with any new drug given over prolonged periods, laboratory parameters should be monitored at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function. In subacute and chronic dog and rat studies designed to produce toxicity, high doses of diltiazem were associated with hepatic damage. In special subacute hepatic studies, oral doses of 125 mg/kg and higher in rats were associated with histalogical changes in the liver which were reversible when the drug was discontinued. In dogs, doses of 20 mg/kg were also associated with hepatic changes, however, these changes were reversible with continued dosing.*
***Drug Interaction.*** *Pharmacologic studies indicate that there may be additive effects in prolonging AV conduction when using beta-blockers or digitalis concomitantly with CARDIZEM. (See WARNINGS.)*
*Controlled and uncontrolled domestic studies suggest that concomitant use of CARDIZEM and beta-blockers or digitalis is usually well tolerated. Available data are not sufficient, however, to predict the effects of concomitant treatment, particularly in patients with left ventricular dysfunction or cardiac conduction abnormalities. In healthy volunteers, diltiazem has been shown to increase serum digoxin levels up to 20%.*
***Carcinogenesis, Mutagenesis, Impairment of Fertility.*** *A 24-month study in rats and a 21-month study in mice showed no evidence of carcinogenicity. There was also no mutagenic response in in vitro bacterial tests. No intrinsic effect on fertility was observed in rats.*
***Pregnancy.*** *Category C. Reproduction studies have been conducted in mice, rats, and rabbits. Administration of doses ranging from five to ten times greater (on a mg/kg basis) than the daily recommended therapeutic dose has resulted in embryo and fetal lethality. These doses, in some studies, have been reported to cause skeletal abnormalities. In the perinatal/postnatal studies, there was some reduction in early individual pup weights and survival rates. There was an increased incidence of stillbirths at doses of 20 times the human dose or greater.*
*There are no well-controlled studies in pregnant women, therefore, use CARDIZEM in pregnant women only if the potential benefit justifies the potential risk to the fetus.*
***Nursing Mothers.*** *Diltiazem is excreted in human milk. One report suggests that concentrations in breast milk may approximate serum levels. If use of CARDIZEM is deemed essential, an alternative method of infant feeding should be instituted.*
***Pediatric Use.*** *Safety and effectiveness in children have not been established.*

***ADVERSE REACTIONS***
*Serious adverse reactions have been rare in studies carried out to date, but it should be recognized that patients with impaired ventricular function and cardiac conduction abnormalities have usually been excluded.*
*In domestic placebo-controlled trials, the incidence of adverse reactions reported during CARDIZEM therapy was not greater than that reported during placebo therapy.*
*The following represent occurrences observed in clinical studies which can be at least reasonably associated with the pharmacology of calcium influx inhibition. In many cases, the relationship to CARDIZEM has not been established. The most common occurrences as well as their frequency of presentation are: edema (2.4%), headache (2.1%), nausea (1.9%), dizziness (1.5%), rash (1.3%), asthenia (1.2%). In addition, the following events were reported infrequently (less than 1%):*

| | |
|---|---|
| *Cardiovascular:* | *Angina, arrhythmia, AV block (first degree), AV block (second or third degree — see conduction warning), bradycardia, congestive heart failure, flushing, hypotension, palpitations, syncope.* |
| *Nervous System:* | *Amnesia, gait abnormality, hallucinations, insomnia, nervousness, paresthesia, personality change, somnolence, tinnitus, tremor.* |
| *Gastrointestinal:* | *Anorexia, constipation, diarrhea, dysgeusia, dyspepsia, mild elevations of alkaline phosphatase, SGOT, SGPT, and LDH (see hepatic warnings), vomiting, weight increase.* |
| *Dermatologic:* | *Petechiae, pruritus, photosensitivity, urticaria.* |
| *Other:* | *Amblyopia, dyspnea, epistaxis, eye irritation, hyperglycemia, nasal congestion, nocturia, osteoarticular pain, polyuria, sexual difficulties.* |

*The following postmarketing events have been reported infrequently in patients receiving CARDIZEM: alopecia, gingival hyperplasia, erythema multiforme, and leukopenia. However, a definitive cause and effect between these events and CARDIZEM therapy is yet to be established.*

*Issued 7/86*

*See complete Professional Use Information before prescribing.*

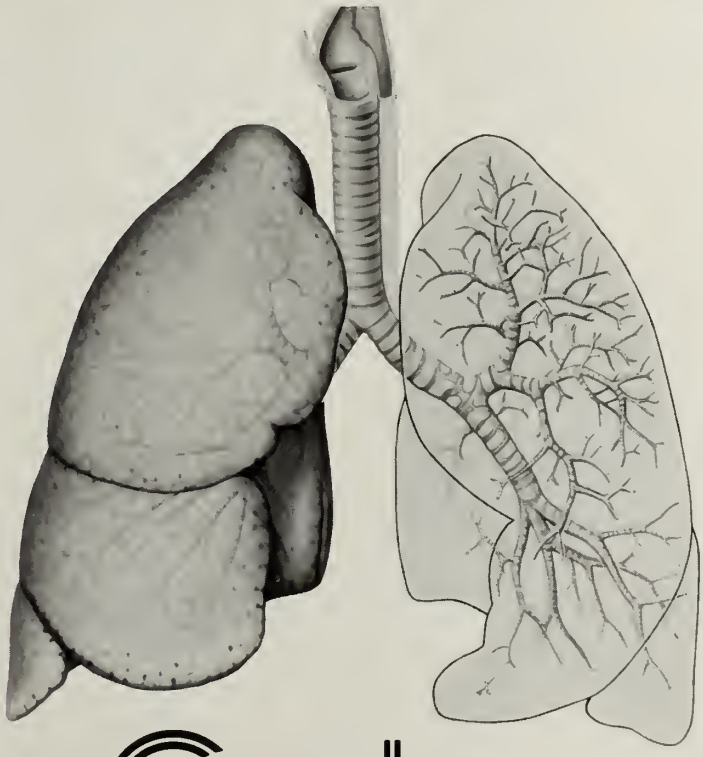
***References:*** ***1.*** *Pepine CJ, Feldman RL, Hill JA, et al: Clinical outcome after treatment of rest angina with calcium blockers. Comparative experience during the initial year of therapy with diltiazem, nifedipine, and verapamil. Am Heart J 1983, 106(6):1341-1347.* ***2.*** *Shapiro W: Calcium channel blockers: Actions on the heart and uses in ischemic heart disease. Consultant 1984,24(Dec):150-159.* ***3.*** *Johnstan DL, Lesoway R, Humen DP, et al: Clinical and hemodynamic evaluation of propranolol in combination with verapamil, nifedipine and diltiazem in exertional angina pectoris: A placebo-controlled, double-blind, randomized, crossover study. Am J Cardiol 1985,55:680-687.* ***4.*** *Cohn PF, Braunwald E: Chronic ischemic heart disease, in Braunwald E (ed): Heart Disease: A Textbook of Cardiovascular Medicine, ed 2. Philadelphia, WB Saunders Co, 1984, chap 39.* ***5.*** *Schroeder JS: Calcium and beta blockers in ischemic heart disease: When to use which. Mod Med 1982,50(Sept):94-116.*

Another potient benefit product from

PHARMACEUTICAL DIVISION
MARION LABORATORIES, INC.
KANSAS CITY, MO 64137

0246M6

# Consider the causative organisms...



# Ceclor®
## cefaclor

## 250-mg Pulvules® t.i.d. offers effectiveness against the major causes of bacterial bronchitis

*Haemophilus influenzae, Streptococcus pneumoniae*
(ampicillin-susceptible and ampicillin-resistant)

*Note:* Ceclor is contraindicated in patients with known allergy to the cephalosporins and should be given cautiously to penicillin-allergic patients.

Penicillin is the usual drug of choice in the treatment and prevention of streptococcal infections, including the prophylaxis of rheumatic fever. See prescribing information.

Ceclor® (cefaclor)

**Summary. Consult the package literature for prescribing information.**

**Indications:** Lower respiratory infections, including pneumonia, caused by susceptible strains of *Streptococcus pneumoniae, Haemophilus influenzae,* and *Streptococcus pyogenes* (group A β-hemolytic streptococci).

**Contraindication:**
Known allergy to cephalosporins.

**Warnings:**
CECLOR SHOULD BE ADMINISTERED CAUTIOUSLY TO PENICILLIN-SENSITIVE PATIENTS. PENICILLINS AND CEPHALOSPORINS SHOW PARTIAL CROSS-ALLERGENICITY. POSSIBLE REACTIONS INCLUDE ANAPHYLAXIS.

Administer cautiously to allergic patients.

Pseudomembranous colitis has been reported with virtually all broad-spectrum antibiotics. It must be considered in differential diagnosis of antibiotic-associated diarrhea. Colon flora is altered by broad-spectrum antibiotic treatment, possibly resulting in antibiotic-associated colitis.

**Precautions:**
- Discontinue Ceclor in the event of allergic reactions to it.
- Prolonged use may result in overgrowth of nonsusceptible organisms.
- Positive direct Coombs' tests have been reported during treatment with cephalosporins.
- Ceclor should be administered with caution in the presence of markedly impaired renal function. Although dosage adjustments in moderate to severe renal impairment are usually not required, careful clinical observation and laboratory studies should be made.
- Broad-spectrum antibiotics should be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis.
- Safety and effectiveness have not been determined in pregnancy, lactation, and infants less than one month old. Ceclor penetrates mother's milk. Exercise caution in prescribing for these patients.

**Adverse Reactions:** (percentage of patients)

Therapy-related adverse reactions are uncommon. Those reported include:
- Gastrointestinal (mostly diarrhea): 2.5%.
- Symptoms of pseudomembranous colitis may appear either during or after antibiotic treatment.
- Hypersensitivity reactions (including morbilliform eruptions, pruritus, urticaria, and serum-sickness-like reactions that have included erythema multiforme [rarely, Stevens-Johnson syndrome] or the above skin manifestations accompanied by arthritis/arthralgia and, frequently, fever): 1.5%; usually subside within a few days after cessation of therapy. Serum-sickness-like reactions have been reported more frequently in children than in adults and have usually occurred during or following a second course of therapy with Ceclor. No serious sequelae have been reported. Antihistamines and corticosteroids appear to enhance resolution of the syndrome.
- Cases of anaphylaxis have been reported, half of which have occurred in patients with a history of penicillin allergy.
- As with some penicillins and some other cephalosporins, transient hepatitis and cholestatic jaundice have been reported rarely.
- Rarely, reversible hyperactivity, nervousness, insomnia, confusion, hypertonia, dizziness, and somnolence have been reported.
- Other: eosinophilia, 2%; genital pruritus or vaginitis, less than 1%; and, rarely, thrombocytopenia.

**Abnormalities in laboratory results of uncertain etiology**
- Slight elevations in hepatic enzymes.
- Transient fluctuations in leukocyte count (especially in infants and children).
- Abnormal urinalysis; elevations in BUN or serum creatinine.
- Positive direct Coombs' test.
- False-positive tests for urinary glucose with Benedict's or Fehling's solution and Clinitest® tablets but not with Tes-Tape® (glucose enzymatic test strip, Lilly).

|072886R|
PA 8794 AMP

©1987, ELI LILLY AND COMPANY

Lilly

*Additional information available to the profession on request from Eli Lilly and Company, Indianapolis, Indiana 46285.*

700241

**Eli Lilly Industries, Inc**
Carolina, Puerto Rico 00630

Glaxo

IN HYPERTENSION

# resistance in the elderly[1]

- ☐ Effective blood pressure control
- ☐ Low incidence of fatigue,[2,3] impotence[2,3] and cold extremities[2-4]

Contraindicated in bronchial asthma, overt cardioc failure, greater-than-first-degree heart block, cardiogenic shock, and severe bradycardia.

See next page for references and Brief Summary of Praduct Informotian, which includes a listing of reparted adverse reactians.

**TRANDATE®** *b.i.d.*

*labetalol HCl/Glaxo* *100 mg/200 mg tablets*

## Because it also vasodilates

**References**: 1. Holtzman JL, Finley O, Johnson B, et al. The effects of single-dose atenolol, labetalol, and propranolol on cardiac and vascular function. *Clin Pharmacol Ther* 1986;40:268-273. 2. Oue OL, Giguere GC, Plachetka JR: Postmarketing comparison of labetalol and propranolol in hypertensive patients. *Clin Ther* 1986;8(6):624-631. 3. Burris JF, Goldstein J, Zager PG, et al: Comparative tolerability of labetalol versus propranolol, atenolol, pindolol, metoprolol, and nadolol. *J Clin Hypertens* 1986;3:1-9. 4. Erb RJ, Plachetka JR: Thermographic evaluation of the peripheral vascular effects of labetalol and propranolol. *Curr Ther Res* 1985;28(1):68-73.

---

**TRANOATE® Tablets**
**(labetalol hydrochloride)**

**BRIEF SUMMARY OF PRODUCT INFORMATION**

The following is a brief summary only. Before prescribing, see complete prescribing information in TRANOATE® Tablets product labeling.

**INOICATIONS AND USAGE:** TRANOATE® Tablets are indicated in the management of hypertension. TRANOATE Tablets may be used alone or in combination with other antihypertensive agents, especially thiazide and loop diuretics.

**CONTRAINDICATIONS:** TRANOATE® Tablets are contraindicated in bronchial asthma, overt cardiac failure, greater-than-first-degree heart block, cardiogenic shock, and severe bradycardia (see **WARNINGS**).

**WARNINGS: Cardiac Failure:** Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure. Beta-blockade carries a potential hazard of further depressing myocardial contractility and precipitating more severe failure. Although beta-blockers should be avoided in overt congestive heart failure, if necessary labetalol HCl can be used with caution in patients with a history of heart failure who are well compensated. Congestive heart failure has been observed in patients receiving labetalol HCl. Labetalol HCl does not abolish the inotropic action of digitalis on heart muscle.

**In Patients Without a History of Cardiac Failure:** In patients with latent cardiac insufficiency, continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or be given a diuretic, and the response should be observed closely. If cardiac failure continues despite adequate digitalization and diuretic, TRANOATE® therapy should be withdrawn (gradually, if possible).

**Exacerbation of Ischemic Heart Disease Following Abrupt Withdrawal:** Angina pectoris has not been reported upon labetalol HCl discontinuation. However, hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred after *abrupt* discontinuation of such therapy. When discontinuing chronically administered TRANDATE, particularly in patients with ischemic heart disease, the dosage should be gradually reduced over a period of one to two weeks and the patient should be carefully monitored. If angina markedly worsens or acute coronary insufficiency develops, TRANOATE administration should be reinstituted promptly, at least temporarily, and other measures appropriate for the management of unstable angina should be taken. Patients should be warned against interruption or discontinuation of therapy without the physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue TRANDATE therapy abruptly even in patients treated only for hypertension.

**Nonallergic Bronchospasm (eg, Chronic Bronchitis and Emphysema): Patients with bronchospastic disease should, in general, not receive beta-blockers.** TRANOATE may be used with caution, however, in patients who do not respond to, or cannot tolerate, other antihypertensive agents. It is prudent, if TRANDATE is used, to use the smallest effective dose, so that inhibition of endogenous or exogenous beta-agonists is minimized.

**Pheochromocytoma:** Labetalol HCl has been shown to be effective in lowering blood pressure and relieving symptoms in patients with pheochromocytoma. However, paradoxical hypertensive responses have been reported in a few patients with this tumor; therefore, use caution when administering labetalol HCl to patients with pheochromocytoma.

**Diabetes Mellitus and Hypoglycemia:** Beta-adrenergic blockade may prevent the appearance of premonitory signs and symptoms (eg, tachycardia) of acute hypoglycemia. This is especially important with labile diabetics. Beta-blockade also reduces the release of insulin in response to hyperglycemia; it may therefore be necessary to adjust the dose of antidiabetic drugs.

**Major Surgery:** The necessity or desirability of withdrawing beta-blocking therapy prior to major surgery is controversial. Protracted severe hypotension and difficulty in restarting or maintaining a heartbeat have been reported with beta-blockers. The effect of labetalol HCl's alpha-adrenergic activity has not been evaluated in this setting.

A synergism between labetalol HCl and halothane anesthesia has been shown (see **Drug Interactions** under **PRECAUTIONS**).

**PRECAUTIONS: General:** ***Impaired Hepatic Function:*** TRANOATE® Tablets should be used with caution in patients with impaired hepatic function since metabolism of the drug may be diminished.

***Jaundice or Hepatic Dysfunction:*** On rare occasions, labetalol HCl has been associated with jaundice (both hepatic and cholestatic). It is therefore recommended that treatment with labetalol HCl be stopped immediately should a patient develop jaundice or laboratory evidence of liver injury. Both have been shown to be reversible on stopping therapy.

**Information for Patients:** As with all drugs with beta-blocking activity, certain advice to patients being treated with labetalol HCl is warranted. This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects. While no incidence of the abrupt withdrawal phenomenon (exacerbation of angina pectoris) has been reported with labetalol HCl, dosing with TRANOATE Tablets should not be interrupted or discontinued without a physician's advice. Patients being treated with TRANOATE Tablets should consult a physician at any sign of impending cardiac failure. Also, transient scalp tingling may occur, usually when treatment with TRANOATE Tablets is initiated (see **ADVERSE REACTIONS**).

**Laboratory Tests:** As with any new drug given over prolonged periods, laboratory parameters should be observed over regular intervals. In patients with concomitant illnesses, such as impaired renal function, appropriate tests should be done to monitor these conditions.

**Drug Interactions:** In one survey, 2.3% of patients taking labetalol HCl in combination with tricyclic antidepressants experienced tremor as compared to 0.7% reported to occur with labetalol HCl alone. The contribution of each of the treatments to this adverse reaction is unknown, but the possibility of a drug interaction cannot be excluded.

Drugs possessing beta-blocking properties can blunt the bronchodilator effect of beta-receptor agonist drugs in patients with bronchospasm; therefore, doses greater than the normal antiasthmatic dose of beta-agonist bronchodilator drugs may be required.

Cimetidine has been shown to increase the bioavailability of labetalol HCl. Since this could be explained either by enhanced absorption or by an alteration of hepatic metabolism of labetalol HCl, special care should be used in establishing the dose required for blood pressure control in such patients.

Synergism has been shown between halothane anesthesia and intravenously administered labetalol HCl. During controlled hypotensive anesthesia using labetalol HCl in association with halothane, high concentrations (3% or above) of halothane should not be used because the degree of hypotension will be increased and because of the possibility of a large reduction in cardiac output and an increase in central venous pressure. The anesthesiologist should be informed when a patient is receiving labetalol HCl.

Labetalol HCl blunts the reflex tachycardia produced by nitroglycerin without preventing its hypotensive effect. If labetalol HCl is used with nitroglycerin in patients with angina pectoris, additional antihypertensive effects may occur.

**Drug/Laboratory Test Interactions:** The presence of a metabolite of labetalol in the urine may result in falsely increased levels of urinary catecholamines when measured by a nonspecific trihydroxyindole (THI) reaction. In screening patients suspected of having a pheochromocytoma and being treated with labetalol HCl, specific radioenzymatic or high performance liquid chromatography assay techniques should be used to determine levels of catecholamines or their metabolites.

**Carcinogenesis, Mutagenesis, Impairment of Fertility:** Long-term oral dosing studies with labetalol HCl for 18 months in mice and for two years in rats showed no evidence of carcinogenesis. Studies with labetalol HCl using dominant lethal assays in rats and mice and exposing microorganisms according to modified Ames tests showed no evidence of mutagenesis.

**Pregnancy:** ***Teratogenic Effects: Pregnancy Category C:*** Teratogenic studies have been performed with labetalol in rats and rabbits at oral doses up to approximately six and four times the maximum recommended human dose (MRHD), respectively. No reproducible evidence of fetal malformations was observed. Increased fetal resorptions were seen in both species at doses approximating the MRHO. There are no adequate and well-controlled studies in pregnant women. Labetalol should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

***Nonteratogenic Effects:*** Infants of mothers who were treated with labetalol HCl during pregnancy did not appear to be adversely affected by the drug. Oral administration of labetalol to rats during late gestation through weaning at doses of two to four times the MRHO caused a decrease in neonatal survival.

**Labor and Oelivery:** Labetalol HCl given to pregnant women with hypertension did not appear to affect the usual course of labor and delivery.

**Nursing Mothers:** Small amounts of labetalol (approximately 0.004% of the maternal dose) are excreted in human milk. Caution should be exercised when TRANOATE Tablets are administered to a nursing woman.

**Pediatric Use:** Safety and effectiveness in children have not been established.

**AOVERSE REACTIONS:** Most adverse effects are mild, transient, and occur early in the course of treatment. In controlled clinical trials of three to four months' duration, discontinuation of TRANOATE® Tablets due to one or more adverse effects was required in 7% of all patients. In these same trials, beta-blocker control agents led to discontinuation in 8% to 10% of patients, and a centrally acting alpha-agonist in 30% of patients.

The following adverse reactions were derived from multi-center, controlled clinical trials over treatment periods of three and four months. The rates, which ranged from less than 1% to 5% except as otherwise noted, are based on adverse reactions considered probably drug-related by the investigator. If all reports are considered, the rates are somewhat higher (eg, dizziness, 20%; nausea, 14%; fatigue, 11%).

***Body as a Whole:*** Fatigue, asthenia, and headache.

***Gastrointestinal:*** Nausea (6%), vomiting, dyspepsia, diarrhea, and taste distortion.

***Central and Peripheral Nervous Systems:*** Dizziness (11%), paresthesia, and drowsiness.

***Autonomic Nervous System:*** Nasal stuffiness, ejaculation failure, impotence, and increased sweating.

***Cardiovascular:*** Edema and postural hypotension.

***Respiratory:*** Dyspnea.

***Skin:*** Rash.

***Special Senses:*** Vision abnormality and vertigo.

The adverse effects were reported spontaneously and are representative of the incidence of adverse effects that may be observed in a properly selected hypertensive patient population, ie, a group excluding patients with bronchospastic disease, overt congestive heart failure, or other contraindications to beta-blocker therapy.

Clinical trials also included studies utilizing daily doses up to 2,400 mg in more severely hypertensive patients. The US therapeutic trials data base for adverse reactions that are clearly or possibly dose-related shows that the following side effects increased with increasing dose: dizziness, fatigue, nausea, vomiting, dyspepsia, paresthesia, nasal stuffiness, ejaculation failure, impotence, and edema.

In addition, a number of other less common adverse events have been reported in clinical trials or the literature:

***Cardiovascular:*** Postural hypotension, including rarely, syncope.

***Central and Peripheral Nervous Systems:*** Paresthesias, most frequently described as scalp tingling. In most cases, it was mild, transient, and usually occurred at the beginning of treatment.

***Collagen Disorders:*** Systemic lupus erythematosus; positive antinuclear factor (ANF).

***Eyes:*** Dry eyes.

***Immunological System:*** Antimitochondrial antibodies.

***Liver and Biliary System:*** Cholestasis with or without jaundice.

***Musculoskeletal System:*** Muscle cramps; toxic myopathy.

***Respiratory System:*** Bronchospasm.

***Skin and Appendages:*** Rashes of various types, such as generalized maculopapular, lichenoid, urticarial, bullous lichen planus, psoriaform, and facial erythema; Peyronie's disease; reversible alopecia.

***Urinary System:*** Difficulty in micturition, including acute urinary bladder retention.

Following approval for marketing in the United Kingdom, a monitored release survey involving approximately 6,800 patients was conducted for further safety and efficacy evaluation of this product. Results of this survey indicate that the type, severity, and incidence of adverse effects were comparable to those cited above.

**Potential Adverse Effects:** In addition, other adverse effects not listed above have been reported with other beta-adrenergic blocking agents.

***Central Nervous System:*** Reversible mental depression progressing to catatonia, an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance or neuropsychometrics.

***Cardiovascular:*** Intensification of AV block (see **CONTRAINDICATIONS**).

***Allergic:*** Fever combined with aching and sore throat; laryngospasm; respiratory distress.

***Hematologic:*** Agranulocytosis; thrombocytopenic or nonthrombocytopenic purpura.

***Gastrointestinal:*** Mesenteric artery thrombosis; ischemic colitis.

The oculomucocutaneous syndrome associated with the beta-blocker practolol has not been reported with labetalol HCl.

**Clinical Laboratory Tests:** There have been reversible increases of serum transaminases in 4% of patients treated with labetalol HCl and tested, and more rarely, reversible increases in blood urea.

**OVERDOSAGE:** Information concerning possible overdosage and its treatment appears in the full prescribing information.

**DOSAGE ANO AOMINISTRATION:** OOSAGE MUST BE INOIVIOUALIZEO. The recommended *initial* dosage is 100 mg *twice* daily whether used alone or added to a diuretic regimen. After two or three days, using standing blood pressure as an indicator, dosage may be titrated in increments of 100 mg bid every two or three days. The usual *maintenance* dosage of labetalol HCl is between 200 and 400 mg *twice* daily. Before use, see complete prescribing information for dosage details.

**HOW SUPPLIEO:** TRANDATE® Tablets, 100 mg, light orange, round, scored, film-coated tablets engraved on one side with "TRANDATE 100 GLAXO," bottles of 100 (NOC 0173-0346-43) and 500 (NOC 0173-0346-44) and unit dose packs of 100 tablets (NOC 0173-0346-47).

TRANOATE Tablets, 200 mg, white, round, scored, film-coated tablets engraved on one side with "TRANOATE 200 GLAXO," bottles of 100 (NOC 0173-0347-43) and 500 (NOC 0173-0347-44) and unit dose packs of 100 tablets (NOC 0173-0347-47).

TRANOATE Tablets, 300 mg, peach, round, scored, film-coated tablets engraved on one side with "TRANOATE 300 GLAXO," bottles of 100 (NOC 0173-0348-43) and 500 (NOC 0173-0348-44) and unit dose packs of 100 tablets (NOC 0173-0348-47).

**TRANDATE Tablets should be stored between 2° and 30°C (36° and 86°F). TRANOATE Tablets in the unit dose boxes should be protected from excessive moisture.**

©Copyright 1984, Glaxo Inc. All rights reserved.

September 1986

Glaxo Inc.
Research Triangle Park, NC 27709

©1987, Glaxo Inc. TRN263 April 1987

# TIME to subscribe

Because time is important to you, **The Western Journal of Medicine** is designed to give you useful information—quickly.

Epitomes of Progress briefly highlights 10 to 12 major advances in a different specialty each month.

**WJM** predicts, examines and evaluates socioeconomic trends in medicine.

Topics in Primary Care Medicine presents articles on common diagnostic or therapeutic problems.

**WJM's** articles are to the point. They cross specialty lines. If time is important to you, **WJM** is the medical journal you need.

WJ6/87

Enclosed is $_____ to cover _____ subscriptions.
Subscription renewal ☐ Regular subscription ☐
Foreign subscription ☐

TO: _____

Street _____

City/State/Zip _____

Specialty _____

Gift Card to read "From _____"

**The Western Journal of Medicine**

Please mail this coupon with enclosed payment to:

**Circulation Department**
P.O. Box 7602, San Francisco, California 94120-7602

Subscriptions, 12 issues Per Year
U.S. and Canada $30 1 year, $50 2 years

All other countries $50 1 year, $90 2 years

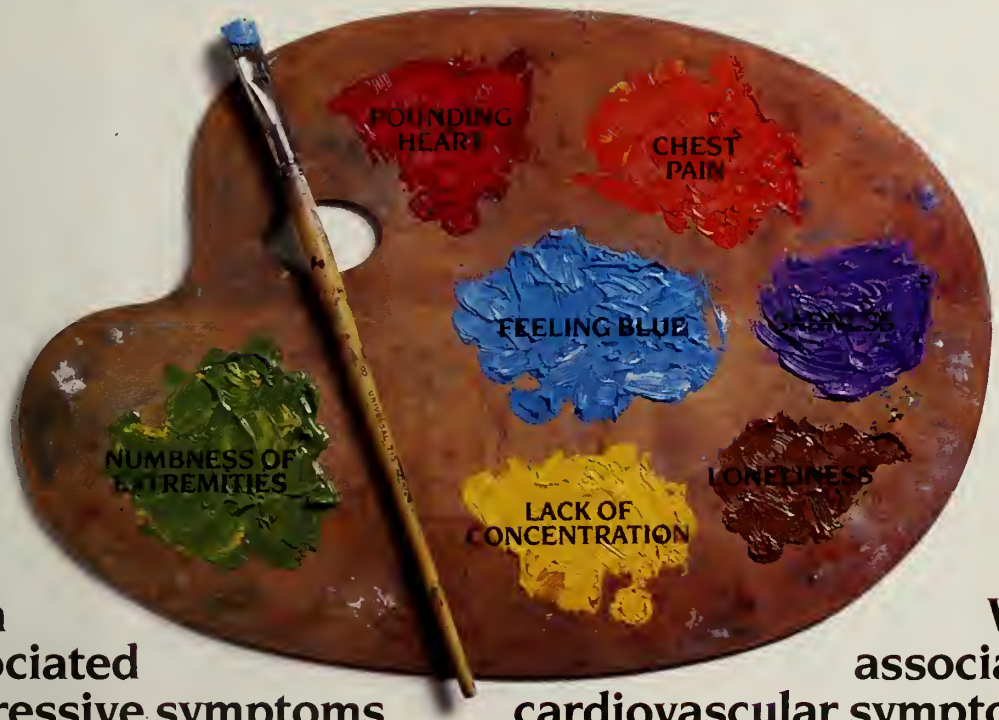
# The portrait of anxiety

Upjohn The Upjohn Company
Kalamazoo, Michigan 49001 USA

Please see adjacent page for brief summary of prescribing information.

© 1987 The Upjohn Company

# is often complicated




## With associated depressive symptoms.

In double-blind, four-week clinical trials in 632 patients with moderate to severe anxiety, therapy with XANAX was compared with placebo.

XANAX was significantly more effective ($P<.001$) than placebo in relieving the anxiety, with over half of the patients showing marked to moderate improvement by the first evaluation period (one week).

In addition, over 70% of these patients experienced associated moderate to severe depressed mood. XANAX was shown to be significantly more effective ($P<.014$) than placebo in improving the associated depressed mood.

## With associated cardiovascular symptoms.

Almost 60% of patients in the study had anxiety with associated cardiovascular symptoms even though cardiovascular disease had been ruled out. XANAX was shown to effectively relieve anxiety including the associated cardiovascular symptoms.

XANAX, the first of a unique class—the triazolobenzodiazepines.

- *Well tolerated*—Side effects, if they occur, are generally observed at the beginning of therapy and usually disappear with continued medication. Drowsiness and light-headedness were the most commonly reported adverse reactions.
- *Sustained efficacy*—No reported increase in dosage during 16-week clinical study, once an appropriate dosage was achieved. Since long-term effectiveness of XANAX has not been established, it is recommended that it not be used for longer than 16 weeks.
- *Simple dosage*—0.25 to 0.5 mg t.i.d.

TABLETS 0.25, 0.5 & 1 MG

# Xanax®

alprazolam IV

## for the relief of complicated anxiety

**XANAX® Tablets**
**(alprazolam) C**

**CONTRAINDICATIONS**
Patients with sensitivity to this drug or other benzodiazepines and in acute narrow angle glaucoma.

**WARNINGS**
Not of value in psychotic patients. Caution patients against hazardous occupations requiring complete mental alertness and about the simultaneous ingestion of alcohol and other CNS depressant drugs.

Benzodiazepines can cause fetal harm in pregnant women. Warn patients of the potential hazard to the fetus. Avoid during the first trimester.

**PRECAUTIONS**
*General*: The dosage of XANAX Tablets should be reduced or withdrawn gradually, since withdrawal seizures have been reported upon abrupt withdrawal. If XANAX is combined with other psychotropics or anticonvulsant drugs, consider drug potentiation (see Drug Interaction section). Exercise the usual precautions regarding size of the prescription for depressed or suicidal patients. In elderly and debilitated patients, use the lowest possible dosage (see Dosage and Administration). Observe the usual precautions in treating patients with impaired renal or hepatic function.

***Information for Patients***: Alert patients about: (a) consumption of alcohol and drugs, (b) possible fetal abnormalities, (c) operating machinery or driving, (d) not increasing dose of the drug due to risk of dependence, (e) not stopping the drug abruptly. *Laboratory Tests*: Not ordinarily required in otherwise healthy patients. *Drug Interactions*: Additive CNS depressant effects with other psychotropics, anticonvulsants, antihistamines, ethanol and other CNS depressants. Pharmacokinetic interactions with other drugs, e.g., cimetidine, have been reported. *Drug/Laboratory Test Interactions*: No consistent pattern for a drug or test. *Carcinogenesis, Mutagenesis, Impairment of Fertility*: No carcinogenic potential or impairment of fertility in rats. *Pregnancy*: See Warnings. *Nonteratogenic Effects*: The child born of a mother on benzodiazepines may be at some risk for withdrawal symptoms and neonatal flaccidity. *Labor and Delivery*: No established use. *Nursing Mothers*: Benzodiazepines are excreted in human milk. Women on XANAX should not nurse. *Pediatric Use*: Safety and effectiveness in children below the age of 18 have not been established.

**ADVERSE REACTIONS**
Side effects are generally observed at the beginning of therapy and usually disappear with continued medication. In the usual patient, the most frequent side effects are likely to be an extension of the pharmacologic activity of XANAX, e.g., drowsiness or lightheadedness.

*Central nervous system*: Drowsiness, lightheadedness, depression, headache, confusion, insomnia, nervousness, syncope, dizziness, akathisia, and tiredness/sleepiness. *Gastrointestinal*: Dry mouth, constipation, diarrhea, nausea/vomiting, and increased salivation. *Cardiovascular*: Tachycardia/palpitations, and hypotension. *Sensory*: Blurred vision. *Musculoskeletal*: Rigidity and tremor. *Cutaneous*: Dermatitis/allergy. *Other side effects*: Nasal congestion, weight gain, and weight loss.

Withdrawal seizures have been reported upon rapid decrease or abrupt discontinuation of XANAX. (See Precautions.)

In addition, the following adverse events have been reported with the use of benzodiazepines: dystonia, irritability, concentration difficulties, anorexia, transient amnesia or memory impairment, loss of coordination, fatigue, sedation, slurred speech, jaundice, musculoskeletal weakness, pruritus, diplopia, dysarthria, changes in libido, menstrual irregularities, incontinence and urinary retention.

Paradoxical reactions such as stimulation, agitation, increased muscle spasticity, sleep disturbances, and hallucinations may occur. Should these occur, discontinue the drug.

During prolonged treatment, periodic blood counts, urinalysis, and blood chemistry analysis are advisable. Minor EEG changes, of unknown significance, have been observed.

**DRUG ABUSE AND DEPENDENCE**
*Physical and Psychological Dependence*: Withdrawal symptoms have occurred following abrupt discontinuance of benzodiazepines. Withdrawal seizures have occurred upon rapid decrease or abrupt discontinuation of therapy. In all patients, dosage should be gradually tapered under close supervision. Patients with a history of seizures or epilepsy should not be abruptly withdrawn from XANAX. Addiction-prone individuals should be under careful surveillance. *Controlled Substance Class*: XANAX is a controlled substance and has been assigned to schedule IV.

**OVERDOSAGE**
Manifestations include somnolence, confusion, impaired coordination, diminished reflexes and coma. No delayed reactions have been reported.

**DOSAGE AND ADMINISTRATION**
Dosage should be individualized.

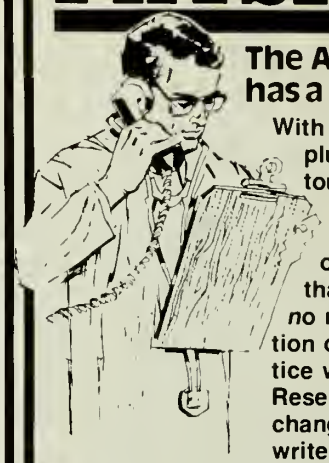
The usual starting dose is 0.25 to 0.5 mg, t.i.d. Maximum total daily dose is 4 mg. In the elderly or debilitated, the usual starting dose is 0.25 mg, two or three times daily. Reduce dosage gradually when terminating therapy, by no more than 0.5 milligram every three days.

**HOW SUPPLIED**
XANAX Tablets are available as 0.25 mg, 0.5 mg, and 1 mg tablets.

**Caution:** Federal law prohibits dispensing without prescription. B-5-S

**Upjohn** THE UPJOHN COMPANY
Kalamazoo, Michigan 49001 USA
J-7384
February 1987

**PHYSICIANS**



**The Air Force Reserve has a position for you!**

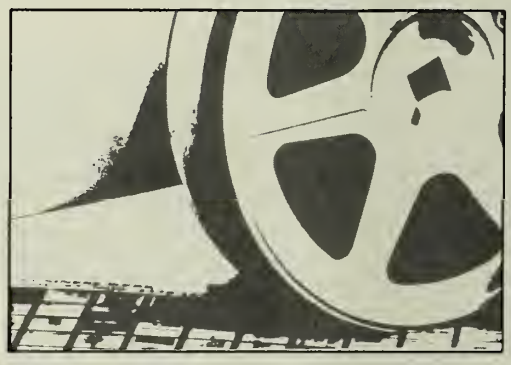
With only one day a month, plus a twelve day annual tour of active duty participation, the Air Force Reserve can offer you the benefits that count! And, there's *no* relocation or interruption of your present practice with your Air Force Reserve association. For a change of pace, call or write the location listed below, providing your name, specialty, phone number, and address.

**Call: 1-912-926-5769 COLLECT**
**To: Health Professions Opportunities**
**P.O. Box 3008**
**Warner Robins, GA 31099**

***AIR FORCE RESERVE*** 26-710-3015

A GREAT WAY TO SERVE

**This Publication is available in Microform.**



**University Microfilms International**

Please send additional information
for _____
(name of publication)
Name_____
Institution_____
Street_____
City_____
State_____ Zip_____

300 North Zeeb Road, Dept P.R., Ann Arbor, Mi. 48106

# 24-hour security for the hypertensive heart

## First-step cardiovascular protection

Reduces workload of the heart by reducing myocardial $O_2$ demand

Preserves $K^+$ balance

Normalizes stress-induced systolic peaks with cardioselective beta-one blockade

Contraindicated in sinus bradycardia, heart block greater than first degree, cardiogenic shock, and overt cardiac failure.

Please consult Brief Summary of Prescribing Information on the following page.

**Once-a-day in hypertension...**

**Lopressor®**
metoprolol tartrate

Changing the Course of Cardiovascular Care

**Geigy**

# First-step protection for the hypertensive heart

**Lopressor®**
metoprolol tartrate USP

**Tablets**
**Ampuls**
**Prefilled Syringes**

*BRIEF SUMMARY (FOR FULL PRESCRIBING INFORMATION, SEE PACKAGE INSERT)*

**CONTRAINDICATIONS**
**Hypertension and Angina**
Lopressor is contraindicated in sinus bradycardia, heart block greater than first degree, cardiogenic shock, and overt cardiac failure (see **WARNINGS**)
**Myocardial Infarction**
Lopressor is contraindicated in patients with a heart rate < 45 beats/min; second- and third-degree heart block; significant first-degree heart block (P-R interval ≥ 0 24 sec), systolic blood pressure < 100 mmHg, or moderate-to-severe cardiac failure (see **WARNINGS**)

**WARNINGS**
**Hypertension and Angina**
***Cardiac Failure:*** Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure, and beta blockade carries the potential hazard of further depressing myocardial contractility and precipitating more severe failure In hypertensive and angina patients who have congestive heart failure controlled by digitalis and diuretics, Lopressor should be administered cautiously Both digitalis and Lopressor slow AV conduction

***In Patients Without a History of Cardiac Failure:*** Continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or given a diuretic The response should be observed closely If cardiac failure continues, despite adequate digitalization and diuretic therapy, Lopressor should be withdrawn

***Ischemic Heart Disease:*** Following abrupt cessation of therapy with certain beta-blocking agents, exacerbations of angina pectoris and, in some cases, myocardial infarction have occurred When discontinuing chronically administered Lopressor, particularly in patients with ischemic heart disease, the dosage should be gradually reduced over a period of 1-2 weeks and the patient should be carefully monitored If angina markedly worsens or acute coronary insufficiency develops, Lopressor administration should be reinstated promptly, at least temporarily, and other measures appropriate for the management of unstable angina should be taken Patients should be warned against interruption or discontinuation of therapy without the physician's advice Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue Lopressor therapy abruptly even in patients treated only for hypertension

***Bronchospastic Diseases:*** **PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD, IN GENERAL, NOT RECEIVE BETA BLOCKERS. Because of its relative beta$_1$ selectivity, however, Lopressor may be used with caution in patients with bronchospastic disease who do not respond to, or cannot tolerate, other antihypertensive treatment. Since beta$_1$ selectivity is not absolute, a beta$_2$-stimulating agent should be administered concomitantly, and the lowest possible dose of Lopressor should be used. In these circumstances it would be prudent initially to administer Lopressor in smaller doses three times daily, instead of larger doses two times daily, to avoid the higher plasma levels associated with the longer dosing interval. (See DOSAGE AND ADMINISTRATION.)**

***Major Surgery:*** The necessity or desirability of withdrawing beta-blocking therapy prior to major surgery is controversial; the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

Lopressor, like other beta blockers, is a competitive inhibitor of beta-receptor agonists, and its effects can be reversed by administration of such agents, e g , dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension Difficulty in restarting and maintaining the heart beat has also been reported with beta blockers

***Diabetes and Hypoglycemia:*** Lopressor should be used with caution in diabetic patients if a beta-blocking agent is required Beta blockers may mask tachycardia occurring with hypoglycemia, but other manifestations such as dizziness and sweating may not be significantly affected

***Thyrotoxicosis:*** Beta-adrenergic blockade may mask certain clinical signs (e g , tachycardia) of hyperthyroidism Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta blockade, which might precipitate a thyroid storm

**Myocardial Infarction**
***Cardiac Failure:*** Sympathetic stimulation is a vital component supporting circulatory function, and beta blockade carries the potential hazard of depressing myocardial contractility and precipitating or exacerbating minimal cardiac failure

During treatment with Lopressor, the hemodynamic status of the patient should be carefully monitored If heart failure occurs or persists despite appropriate treatment, Lopressor should be discontinued

***Bradycardia:*** Lopressor produces a decrease in sinus heart rate in most patients; this decrease is greatest among patients with high initial heart rates and least among patients with low initial heart rates. Acute myocardial infarction (particularly inferior infarction) may in itself produce significant lowering of the sinus rate If the sinus rate decreases to < 40 beats/min, particularly if associated with evidence of lowered cardiac output, atropine (0 25-0 5 mg) should be administered intravenously If treatment with atropine is not successful, Lopressor should be discontinued, and cautious administration of isoproterenol or installation of a cardiac pacemaker should be considered

***AV Block:*** Lopressor slows AV conduction and may produce significant first- (P-R interval ≥0 26 sec), second-, or third-degree heart block Acute myocardial infarction also produces heart block

If heart block occurs, Lopressor should be discontinued and atropine (0 25-0 5 mg) should be administered intravenously If treatment with atropine is not successful, cautious administration of isoproterenol or installation of a cardiac pacemaker should be considered

***Hypotension:*** If hypotension (systolic blood pressure ≤ 90 mmHg) occurs, Lopressor should be discontinued, and the hemodynamic status of the patient and the extent of myocardial damage carefully assessed Invasive monitoring of central venous, pulmonary capillary wedge, and arterial pressures may be required Appropriate therapy with fluids, positive inotropic agents, balloon counterpulsation, or other treatment modalities should be instituted If hypotension is associated with sinus bradycardia or AV block, treatment should be directed at reversing these (see above).

***Bronchospastic Diseases:*** **PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD, IN GENERAL, NOT RECEIVE BETA BLOCKERS. Because of its relative beta$_1$ selectivity, Lopressor may be used with extreme caution in patients with bronchospastic disease. Because it is unknown to what extent beta$_2$-stimulating agents may exacerbate myocardial ischemia and the extent of infarction, these agents should *not* be used prophylactically. If bronchospasm not related to congestive heart failure occurs, Lopressor should be discontinued. A theophylline derivative or a beta$_2$ agonist may be administered cautiously, depending on the clinical condition of the patient. Both theophylline derivatives and beta$_2$ agonists may produce serious cardiac arrhythmias.**

**PRECAUTIONS**
**General**
Lopressor should be used with caution in patients with impaired hepatic function.
**Information for Patients**
Patients should be advised to take Lopressor regularly and continuously, as directed, with or immediately following meals If a dose should be missed, the patient should take only the next scheduled dose (without doubling it). Patients should not discontinue Lopressor without consulting the physician

Patients should be advised (1) to avoid operating automobiles and machinery or engaging in other tasks requiring alertness until the patient's response to therapy with Lopressor has been determined, (2) to contact the physician if any difficulty in breathing occurs, (3) to inform the physician or dentist before any type of surgery that he or she is taking Lopressor
**Laboratory Tests**
Clinical laboratory findings may include elevated levels of serum transaminase, alkaline phosphatase, and lactate dehydrogenase
**Drug Interactions**
Catecholamine-depleting drugs (e g , reserpine) may have an additive effect when given with beta-blocking agents Patients treated with Lopressor plus a catecholamine depletor should therefore be closely observed for evidence of hypotension or marked bradycardia, which may produce vertigo, syncope, or postural hypotension
**Carcinogenesis, Mutagenesis, Impairment of Fertility**
Long-term studies in animals have been conducted to evaluate carcinogenic potential In 2-year studies in rats at three oral dosage levels of up to 800 mg/kg per day, there was no increase in the development of spontaneously occurring benign or malignant neoplasms of any type The only histologic changes that appeared to be drug related were an increased incidence of generally mild focal accumulation of foamy macrophages in pulmonary alveoli and a slight increase in biliary hyperplasia Neither finding represents symptoms of a known disease entity in man. In a 21-month study in Swiss albino mice at three oral dosage levels of up to 750 mg/kg per day, benign lung tumors (small adenomas) occurred more frequently in female mice receiving the highest dose than in untreated control animals. There was no increase in malignant or total (benign plus malignant) lung tumors, nor in the overall incidence of tumors or malignant tumors This 21-month study was repeated in CD-1 mice, and no statistically or biologically significant differences were observed between treated and control mice of either sex for any type of tumor

All mutagenicity tests performed (a dominant lethal study in mice, chromosome studies in somatic cells, a Salmonella/mammalian-microsome mutagenicity test, and a nucleus anomaly test in somatic interphase nuclei) were negative

No evidence of impaired fertility due to Lopressor was observed in a study performed in rats at doses up to 55 5 times the maximum daily human dose of 450 mg
**Pregnancy Category C**
Lopressor has been shown to increase postimplantation loss and decrease neonatal survival in rats at doses up to 55 5 times the maximum daily human dose of 450 mg Distribution studies in mice confirm exposure of the fetus when Lopressor is administered to the pregnant animal. These studies have revealed no evidence of impaired fertility or teratogenicity There are no adequate and well-controlled studies in pregnant women Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed
**Nursing Mothers**
Lopressor is excreted in breast milk in very small quantity An infant consuming 1 liter of breast milk daily would receive a dose of less than 1 mg of the drug Caution should be exercised when Lopressor is administered to a nursing woman
**Pediatric Use**
Safety and effectiveness in children have not been established

**ADVERSE REACTIONS**
**Hypertension and Angina**
Most adverse effects have been mild and transient.

***Central Nervous System:*** Tiredness and dizziness have occurred in about 10 of 100 patients Depression has been reported in about 5 of 100 patients. Mental confusion and short-term memory loss have been reported Headache, nightmares, and insomnia have also been reported

***Cardiovascular:*** Shortness of breath and bradycardia have occurred in approximately 3 of 100 patients Cold extremities, arterial insufficiency, usually of the Raynaud type; palpitations, congestive heart failure, peripheral edema; and hypotension have been reported in about 1 of 100 patients (See **CONTRAINDICATIONS, WARNINGS,** and **PRECAUTIONS** )

***Respiratory:*** Wheezing (bronchospasm) and dyspnea have been reported in about 1 of 100 patients (see **WARNINGS**)

***Gastrointestinal:*** Diarrhea has occurred in about 5 of 100 patients Nausea, dry mouth, gastric pain, constipation, flatulence, and heartburn have been reported in about 1 of 100 patients

***Hypersensitive Reactions:*** Pruritus or rash have occurred in about 5 of 100 patients Worsening of psoriasis has also been reported

***Miscellaneous:*** Peyronie's disease has been reported in fewer than 1 of 100,000 patients Musculoskeletal pain, blurred vision, and tinnitus have also been reported.

There have been rare reports of reversible alopecia, agranulocytosis, and dry eyes Discontinuation of the drug should be considered if any such reaction is not otherwise explicable

The oculomucocutaneous syndrome associated with the beta blocker practolol has not been reported with Lopressor.
**Myocardial Infarction**
***Central Nervous System:*** Tiredness has been reported in about 1 of 100 patients Vertigo, sleep disturbances, hallucinations, headache, dizziness, visual disturbances, confusion, and reduced libido have also been reported, but a drug relationship is not clear

***Cardiovascular:*** In the randomized comparison of Lopressor and placebo described in the **CLINICAL PHARMACOLOGY** section, the following adverse reactions were reported:

| | *Lopressor* | *Placebo* |
|---|---|---|
| Hypotension (systolic BP < 90 mmHg) | 27 4% | 23 2% |
| Bradycardia (heart rate < 40 beats/min) | 15 9% | 6 7% |
| Second- or third-degree heart block | 4 7% | 4 7% |
| First-degree heart block (P-R ≥ 0 26 sec) | 5 3% | 1 9% |
| Heart failure | 27 5% | 29 6% |

***Respiratory:*** Dyspnea of pulmonary origin has been reported in fewer than 1 of 100 patients

***Gastrointestinal:*** Nausea and abdominal pain have been reported in fewer than 1 of 100 patients

***Dermatologic:*** Rash and worsened psoriasis have been reported, but a drug relationship is not clear.

***Miscellaneous:*** Unstable diabetes and claudication have been reported, but a drug relationship is not clear.
**Potential Adverse Reactions**
A variety of adverse reactions not listed above have been reported with other beta-adrenergic blocking agents and should be considered potential adverse reactions to Lopressor

***Central Nervous System:*** Reversible mental depression progressing to catatonia, an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics

***Cardiovascular:*** Intensification of AV block (see **CONTRAINDICATIONS**).

***Hematologic:*** Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

***Hypersensitive Reactions:*** Fever combined with aching and sore throat, laryngospasm, and respiratory distress

**OVERDOSAGE**
**Acute Toxicity**
Several cases of overdosage have been reported, some leading to death

Oral $LD_{50}$'s (mg/kg) mice, 1158-2460, rats, 3090-4670
**Signs and Symptoms**
Potential signs and symptoms associated with overdosage with Lopressor are bradycardia, hypotension, bronchospasm, and cardiac failure
**Treatment**
There is no specific antidote

In general, patients with acute or recent myocardial infarction may be more hemodynamically unstable than other patients and should be treated accordingly (see **WARNINGS, Myocardial Infarction**)

On the basis of the pharmacologic actions of Lopressor, the following general measures should be employed.

***Elimination of the Drug:*** Gastric lavage should be performed

***Bradycardia:*** Atropine should be administered. If there is no response to vagal blockade, isoproterenol should be administered cautiously

***Hypotension:*** A vasopressor should be administered, e g , levarterenol or dopamine

***Bronchospasm:*** A beta$_2$-stimulating agent and/or a theophylline derivative should be administered

***Cardiac Failure:*** A digitalis glycoside and diuretic should be administered. In shock resulting from inadequate cardiac contractility, administration of dobutamine, isoproterenol, or glucagon may be considered

**Geigy**
GEIGY Pharmaceuticals
Division of CIBA-GEIGY Corporation
Ardsley, New York 10502

© 1986, Geigy. (9/86) 536-8180-A 8 C86-36 (Rev 6/86)

# The New Look of

# Medrol® Dosepak™ Unit of Use

## 4 mg methylprednisolone tablets, USP

The explicit printed dosage instructions that accompany each *Dosepak* make it easy for the patient to understand and follow the dosage regimen.

Upjohn 100 A Century of Caring 1886·1986

J-5945RC
January 1986

© 1986 The Upjohn Company

# Continuing Medical Education

ARIZONA • CALIFORNIA, HAWAII, NEVADA • IDAHO • MONTANA • NEW MEXICO • UTAH • WASHINGTON • WYOMING

## ARIZONA

The following list of continuing medical education programs in Arizona is compiled by the Arizona Medical Association. All courses listed have been certified as meeting the criteria for Category I of the ArMA CME Certificate and the AMA Physicians Recognition Award. To list Category I continuing medical education programs, please send information to Arizona Medical Association, 810 West Bethany Home Road, Phoenix, AZ 85013; or phone (602) 246-8901.

Brochures and registration forms are available from the contact person or organization sponsoring the program.

July 24-26—**Coconino County Medical Society Summer Medical Seminar and Day of Surgery.** DuBois Conference Center at Northern Arizona University, Flagstaff. Fri-Sun. Contact: Coconino County Medical Society, (602) 774-7694.

### CONTACT INFORMATION

ArMA—Contact: Arizona Medical Association, 810 W Bethany Home Rd, Phoenix, AZ 85013. (602) 246-8901.

U of A—Contact: University of Arizona College of Medicine, Arizona Health Sciences Center, Tucson, AZ 85724. (602) 626-6707.

## CALIFORNIA, HAWAII AND NEVADA

This listing of continuing education programs in California, Hawaii and Nevada is supplied by the Committee on Continuing Medical Education of the California Medical Association. All courses and meetings listed have been approved for Category I credit toward the CMA Certificate in Continuing Medical Education. To have accredited courses listed here, please send information at least two months in advance to Department of Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690; or phone (415) 863-5522. For a list of organizations approved for Category I credit toward the CMA Certificate in Continuing Medical Education or for more information on accreditation or certification, please write to the above address.

### ANESTHESIOLOGY

June 25-28—**California Society of Anesthesiologists Annual Meeting.** Hotel Inter-Continental, San Diego. Thurs-Sun. 16 hrs. $225. Contact: Linda P. Londerville, 100 S Ellsworth Ave, Ste 806, San Mateo 94401. (415) 348-1407.

August 23-28—**California Society of Anesthesiologists Hawaiian Seminar.** Sheraton Royal Waikoloa Hotel, The Big Island, Hawaii. Sun-Fri. 20 hrs. $375. Contact: Linda P. Londerville, 100 S Ellsworth Ave, Ste 806, San Mateo 94401. (415) 348-1407.

September 12-13—**Case Conference on Clinical Anesthesiology.** California Society of Anesthesiologists at High Sierra Hotel, Lake Tahoe, Nevada. Sat-Sun. 9 hrs. $160. Contact: California Society of Anesthesiologists, 100 S Ellsworth Ave, Ste 806, San Mateo 94401. (415) 348-1407.

October 18-23—**Hawaiian Seminar on Clinical Anesthesia.** California Society of Anesthesiology at Westin Maui, Kaanapali Beach, Hawaii. Sun-Fri. 20 hrs. $375. Contact: California Society of Anesthesiology, 100 S Ellsworth Ave, Ste 806, San Mateo 94401. (415) 348-1407.

### CANCER

September 12—**Advances in Lung Cancer.** UCI at Long Beach. Sat. Contact: UCI.

October 19-21—**11th Annual Cancer Symposium.** Scripps Memorial Hospital at Sheraton Harbor Island Hotel, San Diego. Mon-Wed. 21 hrs. $350. Contact: Nomi Feldman, Scripps Memorial Hospital, 3770 Tansy, San Diego 92121. (619) 453-6222.

### CARDIOLOGY

June 18-20—**Coronary Heart Disease: Current Concepts.** Medical Education Resources at Sheraton Waikiki Hotel, Honolulu, Hawaii. Thurs-Sat. 11 hrs. $295. Contact: Debbie Wilderson, Medical Education Resources, 5808 S Rapp St, Ste 202, Littleton, CO 80120. (800) 421-3756.

June 25-27—**Consultative Cardiology: Update in Diagnostic and Therapeutic Techniques.** American College of Cardiology at Westin South Coast Hotel, Costa Mesa. Thurs-Sat. Contact: Mary Anne McInerny, ACC, 9111 Old Georgetown Rd, Bethesda, MD 20814. (301) 897-5400, ext 226.

### KEY TO ABBREVIATIONS

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690. (415) 863-5522.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Herbert M. Thomas, MD, MPH, Director of CME, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th Street, Los Angeles 90059. (213) 603-3183.

LLU: Loma Linda University
Contact: Varner J. Johns, Jr, MD, Associate Dean for Continuing Medical Education, Loma Linda University School of Medicine, Loma Linda 92354. (714) 796-7311, ext 2400.

PMC: Pacific Medical Center
Contact: Continuing Education, Pacific Medical Center, PO Box 7999, San Francisco 94120. (415) 563-4321, ext 2761.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Medical School Office Building, Suite X-365, Stanford 94305-6114. (415) 723-5594.

UCD: University of California, Davis
Contact: Ruth Feryok, Director, Office of Continuing Medical Education, University of California, Davis, School of Medicine, 2701 Stockton Boulevard, Sacramento 95817. (916) 453-5390.

UCI: University of California, Irvine
Contact: Melvin I. Marks, MD, Assistant Dean, University of California, Irvine, California College of Medicine, c/o UCI/CME Program, Memorial Medical Center, 2801 Atlantic Avenue, Long Beach 90801-1428. (213) 595-3811, or (714) 856-5414, UCI Extension.

UCLA: University of California, Los Angeles
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, PO Box 24902, UCLA, Los Angeles 90024. (213) 825-7241.

UCSD: University of California, San Diego
Contact: Office of Continuing Medical Education, University of California, San Diego, School of Medicine (M-017), La Jolla 92093. (619) 534-3713.

UCSF: University of California, San Francisco
Contact: Robert Maggio, Administrative Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 476-4251.

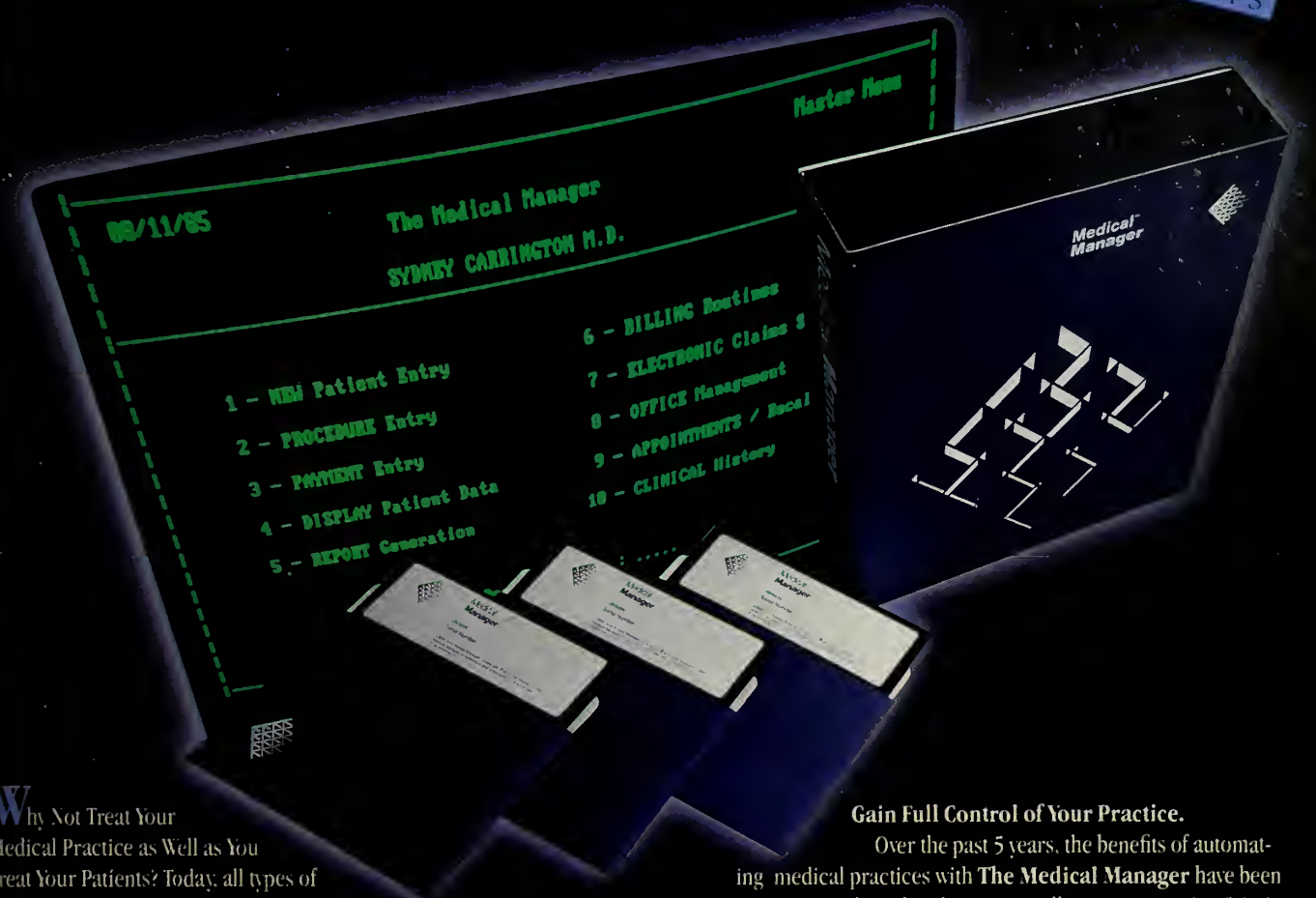
USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 1975 Zonal Ave, KAM314, Los Angeles 90033. (213) 224-7051.

*(Continued on Page 784)*

# Medical Manager®

## Medical Office Management Software

NOW AVAILABLE FOR UNIX SYSTEMS




Why Not Treat Your Medical Practice as Well as You Treat Your Patients? Today, all types of businesses are using computer systems to enhance productivity. As business professionals, more and more physicians are looking to computer systems to dramatically improve productivity and generate timely information for sound financial management and superior patient care.

**Join the Information Revolution.**

Automate your business with a complete medical practice management solution from Systems Plus, Inc. **The Medical Manager** software manages your practice from the moment a new patient calls for an appointment through to billing and patient recall.

- **Comprehensive features** for all aspects of patient communications including encounter forms, insurance billing, outstanding balance follow-up and more...
- **Accountability** — provides sound financial data and clear audit trails based on standard accounting principles.
- **Reporting** — creates detailed office management and financial reports; Custom reports generator.
- **Electronic Media Claims (EMC)** increases cash flow by reducing insurance payment turnaround times. The EMC module submits and tracks insurance claims via modem or diskette to insurance companies nationwide.
- **Flexibility** — supports popular hardware and operating environments including PC-DOS,* Concurrent PC DOS,* Xenix,* Novell NetWare* and Unix.*

**Gain Full Control of Your Practice.**

Over the past 5 years, the benefits of automating medical practices with **The Medical Manager** have been proven in 2,500 single and multi-user installations supporting 8,000 physicians nationwide. Thousands of your colleagues have increased efficiency, productivity, and profitability while gaining tighter control over the day-to-day operations of their businesses.

Find out how Systems Plus, the national leader in computer solutions for practice management, can help you survive in today's competitive medical marketplace by turning your practice into a well-managed business. Contact us on our toll-free lines at **(800) 222-7701 or (800) 222-7707 in California** for more information and the name of your local representative. Mention this ad and receive a **free** copy of our Medical Manager features and reports manual.

**Systems Plus, Inc.®**
500 Clyde Avenue
Mountain View, CA 94043
(415) 969-7047

Systems Plus is a registered trademark of Systems Plus, Inc. • Medical Manager is a registered trademark of Personalized Programming, Inc. • Unix is a trademark of AT&T Bell Lab. • Novell NetWare is a registered trademark of Novell, Inc. • PC-DOS is a registered trademark of IBM. • Concurrent PC DOS is a registered trademark of Digital Research, Inc. • Xenix is a registered trademark of Microsoft Corporation.

# Motrin® 800 mg TABLETS

ibuprofen

## a stronger reason to prescribe Motrin Tablets

© 1986 The Upjohn Company

# Motrin® 800 TABLETS mg
ibuprofen

## Extra-Strength Motrin Tablets— a convenient way to tap the full potential of Motrin:

**The newest strength of *Motrin* Tablets**

**makes treatment easier** for arthritis patients who need the doses that provide higher levels of anti-inflammatory activity as well as potent analgesia...just 1 tablet t.i.d. provides 2400 mg/day.

**expands the dosage convenience** of MOTRIN Tablets – makes it even easier to adjust the dosage of MOTRIN to each patient's needs...the dosage range of up to 3200 mg/day can be achieved on a q.i.d. regimen. Gastroscopic studies at varying doses show an increased tendency toward gastric irritation at higher doses. However, at comparable doses, gastric irritation is about half that seen with aspirin.

**provides economy...**patients should pay less for MOTRIN Tablets than for comparable dosages of sulindac, piroxicam, or naproxen.

**provides, above all, the experience-proven efficacy and safety profile of *Motrin.*** MOTRIN continues to be America's most often prescribed nonsteroidal anti-inflammatory agent.

Please see adjacent page for a brief summary of prescribing information.

Upjohn 100 A Century of Caring 1886·1986

**MOTRIN® Tablets**
(ibuprofen)

**CONTRAINDICATIONS:** Anaphylactoid reactions have occurred in individuals hypersensitive to MDTRIN or with the syndrome of nasal polyps, angioedema and bronchospastic reactivity to aspirin or other nonsteroidal anti-inflammatory agents.

**WARNINGS:** Peptic ulceration and G.I. bleeding, sometimes severe, have been reported. Ulceration, perforation and bleeding may end fatally. An association has not been established. Use MDTRIN under close supervision in patients with a history of upper gastrointestinal tract disease, after consulting ADVERSE REACTIONS. In patients with active peptic ulcer and active rheumatoid arthritis, try nonulcerogenic drugs, such as gold. If MDTRIN is used, observe the patient closely for signs of ulcer perforation or G.I. bleeding.

**PRECAUTIONS:** Blurred and/or diminished vision, scotomata, and/or changes in color vision have been reported. If these develop, discontinue MDTRIN and the patient should have an ophthalmologic examination, including central visual fields and color vision testing.

Fluid retention and edema have been associated with MDTRIN; use with caution in patients with a history of cardiac decompensation or hypertension.

MDTRIN can inhibit platelet aggregation and prolong bleeding time. Use with caution in persons with intrinsic coagulation defects and on anticoagulant therapy.

Patients should report signs or symptoms of gastrointestinal ulceration or bleeding, blurred vision, skin rash, weight gain, or edema.

Patients on prolonged corticosteroid therapy should have therapy tapered slowly when MOTRIN is added.

The antipyretic, anti-inflammatory activity of MDTRIN may mask inflammation and fever.

As with other nonsteroidal anti-inflammatory drugs, borderline elevations of liver tests may occur in up to 15% of patients. These abnormalities may progress, may remain essentially unchanged, or may be transient with continued therapy. Meaningful elevations of SGPT or SGDT (AST) occurred in controlled clinical trials in less than 1% of patients. Severe hepatic reactions, including jaundice and cases of fatal hepatitis, have been reported with ibuprofen as with other nonsteroidal anti-inflammatory drugs. If liver disease develops or if systemic manifestations occur (e.g. eosinophilia, rash, etc.), MOTRIN should be discontinued.

In cross-study comparisons with 1200 mg to 3200 mg daily for several weeks, a slight dose-response decrease in hemoglobin/hematocrit was noted. The total decrease in hemoglobin usually does not exceed 1 gram.

**Renal Effects:** Long term administration of ibuprofen and other NSAID's to animals has resulted in renal papillary necrosis and other abnormal renal pathology. In humans, there have been reports of acute interstitial nephritis with hematuria, proteinuria, and occasionally nephrotic syndrome. In patients with prerenal conditions and reduced renal blood flow or blood volume, NSAID's may precipitate overt renal decompensation. Patients with impaired renal function, heart failure, liver dysfunction, those taking diuretics and the elderly are at greatest risk. Discontinuation of NSAID therapy is typically followed by recovery to the pretreatment state.

In patients with renal impairment, reduced dosage may be necessary. Prospective studies of MOTRIN safety in patients with chronic renal failure have not been done.

**Drug Interactions: Aspirin:** Used concomitantly may decrease MDTRIN blood levels.

**Coumarin:** Bleeding has been reported in patients taking MOTRIN and coumarin.

**Pregnancy and nursing mothers:** MDTRIN should not be taken during pregnancy or by nursing mothers.

**ADVERSE REACTIONS:** The most frequent type of adverse reaction occurring with MDTRIN is gastrointestinal of which one or more occurred in 4% to 16% of the patients. Reported side effects were higher at 3200 than at 2400 mg/day or less.

***Incidence Greater than 1% (but less than 3%) – Probable Causal Relationship***

**GASTROINTESTINAL:** Nausea,* epigastric pain,* heartburn,* diarrhea, abdominal distress, nausea and vomiting, indigestion, constipation, abdominal cramps or pain, fullness of GI tract (bloating and flatulence); **CENTRAL NERVOUS SYSTEM:** Dizziness,* headache, nervousness; **DERMATOLOGIC:** Rash* (including maculopapular type), pruritus; **SPECIAL SENSES:** Tinnitus; **METABOLIC/ENDOCRINE:** Decreased appetite; **CARDIOVASCULAR:** Edema, fluid retention (generally responds promptly to drug discontinuation; see PRECAUTIONS).

***Incidence less than 1% Probable Causal Relationship****

**GASTROINTESTINAL:** Gastric or duodenal ulcer with bleeding and/or perforation, gastrointestinal hemorrhage, melena, gastritis, hepatitis, jaundice, abnormal liver function tests; **CENTRAL NERVOUS SYSTEM:** Depression, insomnia, confusion, emotional lability, somnolence, aseptic meningitis with fever and coma; **DERMATOLOGIC:** Vesiculobullous eruptions, urticaria, erythema multiforme, Stevens-Johnson syndrome, alopecia; **SPECIAL SENSES:** Hearing loss, amblyopia (blurred and/or diminished vision, scotomata and/or changes in color vision) (see PRECAUTIDNS); **HEMATOLOGIC:** Neutropenia, agranulocytosis, aplastic anemia, hemolytic anemia (sometimes Coombs positive), thrombocytopenia with or without purpura, eosinophilia, decreases in hemoglobin and hematocrit (see PRECAUTIONS); **CARDIOVASCULAR:** Congestive heart failure in patients with marginal cardiac function, elevated blood pressure, palpitations; **ALLERGIC:** Syndrome of abdominal pain, fever, chills, nausea and vomiting; anaphylaxis, bronchospasm (see CDNTRAINDICATIONS); **RENAL:** Acute renal failure in patients with pre-existing significantly impaired renal function, decreased creatinine clearance, polyuria, azotemia, cystitis, hematuria; **MISCELLANEOUS:** Dry eyes and mouth, gingival ulcer, rhinitis.

***Incidence less than 1% – Causal Relationship Unknown****

**GASTROINTESTINAL:** Pancreatitis; **CENTRAL NERVOUS SYSTEM:** Paresthesias, hallucinations, dream abnormalities, pseudotumor cerebri; **DERMATOLOGIC:** Toxic epidermal necrolysis, photoallergic skin reactions; **SPECIAL SENSES:** Conjunctivitis, diplopia, optic neuritis, cataracts; **HEMATOLOGIC:** Bleeding episodes (e.g. epistaxis, menorrhagia); **METABOLIC/ENDOCRINE:** Gynecomastia, hypoglycemic reaction, acidosis; **CARDIOVASCULAR:** Arrhythmias (sinus tachycardia, sinus bradycardia); **ALLERGIC:** Serum sickness, lupus erythematosus syndrome, Henoch-Schonlein vasculitis, angioedema; **RENAL:** Renal papillary necrosis.

*Reactions occurring in 3% to 9% of patients treated with MDTRIN. (Those reactions occurring in less than 3% of the patients are unmarked).

**Reactions are classified under **"Probable Causal Relationship (PCR)"** if there has been one positive rechallenge or if three or more cases occur which might be causally related. Reactions are classified under **"Causal Relationship Unknown"** if seven or more events have been reported but the criteria for PCR have not been met.

**OVERDOSAGE:** In cases of acute overdosage, the stomach should be emptied. The drug is acidic and excreted in the urine so alkaline diuresis may be beneficial.

**DOSAGE AND ADMINISTRATION:** Do not exceed 3200 mg/day.

Rheumatoid and osteoarthritis: Suggested dosage is 1200 to 3200 mg per day (400, 600 or 800 mg t.i.d. or q.i.d.). The smallest effective dosage should be used. Mild to moderate pain: 400 mg every 4 to 6 hours as necessary.

**HOW SUPPLIED:**

| MOTRIN Tablets, 400 mg (orange) | MOTRIN Tablets, 600 mg (peach) | MOTRIN Tablets, 800 mg (apricot) |
|---|---|---|
| Bottles of 500 | Bottles of 500 | Bottles of 100 |
| Unit-dose package of 100 | Unit-dose package of 100 | Bottles of 500 |
| Unit of Use bottles of 100 | Unit of Use bottles of 100 | |

**CAUTION:** FEDERAL LAW PRDHIBITS DISPENSING WITHDUT PRESCRIPTION.

**For additional product information, see your Upjohn representative or consult the package insert.**

MED B-9-S

Upjohn 100 A Century of Caring 1886·1986

February 1986
J-6321

# ROCKY MOUNTAIN RURAL TRAUMA SYMPOSIUM

## Montana State University Bozeman, Montana August 3-5, 1987

### The Symposium

The Rocky Mountain Rural Trauma Symposium is the first trauma symposium designed to address the unique needs of physicians and nurses practicing in rural areas. An outstanding visiting faculty of trauma specialists is teamed with the finest Montana physicians and nurses to assure a consistent rural focus in the workshops and meetings. The goal of this symposium is to provide professionals who face severe trauma infrequently in environments where resources are limited with the most current knowledge of trauma care as well as practical application in the rural setting.

### Credits

Montana State University has approved this symposium for 17 CEUs. Application has been made to all appropriate CME providers.

### Sponsors

AHEC-A Regional Partner of the University of Washington School of Medicine; Montana State University; Montana Committee on Trauma; Montana EMS Bureau.

### Offered in Cooperation With

The Departments of Surgery
University of Washington School of Medicine
Oregon Health Sciences University

### For More Information and Program

Contact Continuing Education for the Health Professional, 303 Montana Hall, Montana State University, Bozeman, MT 59717.

### FEES

**$350 for physicians, $180 for nurses.**

# CNA has a longstanding commitment to medical malpractice protection.

The CNA Insurance Companies have been committed to providing quality malpractice insurance for over 15 years. And, we've kept this commitment even through the years of malpractice crises.

One reason we're able to honor that longstanding commitment is our financial strength. CNA has grown to the 14th largest insurance organization. And, we're now one of the largest malpractice insurers. By protecting thousands of medical professionals, we have solid expertise in underwriting, claims service and legal defense.

We've made a commitment to offer comprehensive, quality medical malpractice protection to meet the needs of physicians. For more information, contact the CNA program administrator today.

Fred S. James & Co. of Idaho
380 E. Park Center Boulevard
Boise, ID 83707
(208) 342-6573

The CNA Physicians Protection Program is underwritten by Continental Casualty Company, one of the CNA Insurance Companies.

CNA
For All the Commitments You Make®

# A better alternative for hypertensives who are going bananas...

*Spare your patients the extra cost—in calories, sodium and dollars.*

*Spare your patients the rigors of dietary $K^+$ supplementation.*

# DYAZIDE®

**25 mg** Hydrochlorothiazide/**50 mg** Triamterene/SKF

## Effective antihypertensive* therapy...without the bananas

* Not for initial therapy. See brief summary.

***Before prescribing, see complete prescribing information in SK&F CO. literature or PDR. The following is a brief summary.***

*

***WARNING***

*This drug is not indicated for initial therapy of edema or hypertension. Edema or hypertension requires therapy titrated to the individual. If this combination represents the dosage so determined, its use may be more convenient in patient management. Treatment of hypertension and edema is not static, but must be reevaluated as conditions in each patient warrant.*

***Contraindications:*** *Concomitant use with other potassium-sparing agents such as spironolactone or amiloride. Further use in anuria, progressive renal or hepatic dysfunction, hyperkalemia. Pre-existing elevated serum potassium. Hypersensitivity to either component or other sulfonamide-derived drugs.*

***Warnings:*** *Do not use potassium supplements, dietary or otherwise, unless hypokalemia develops or dietary intake of potassium is markedly impaired. If supplementary potassium is needed, potassium tablets should not be used. Hyperkalemia can occur, and has been associated with cardiac irregularities. It is more likely in the severely ill, with urine volume less than one liter/day, the elderly and diabetics with suspected or confirmed renal insufficiency. Periodically, serum $K^+$ levels should be determined. If hyperkalemia develops, substitute a thiazide alone, restrict $K^+$ intake. Associated widened QRS complex or arrhythmia requires prompt additional therapy. Thiazides cross the placental barrier and appear in cord blood. Use in pregnancy requires weighing anticipated benefits against possible hazards, including fetal or neonatal jaundice, thrombocytopenia, other adverse reactions seen in adults. Thiazides appear and triamterene may appear in breast milk. If their use is essential, the patient should stop nursing. Adequate information on use in children is not available. Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma. Possible exacerbation or activation of systemic lupus erythematosus has been reported with thiazide diuretics.*

***Precautions:*** *The bioavailability of the hydrochlorothiazide component of 'Dyazide' is about 50% of the bioavailability of the single entity. Theoretically, a patient transferred from the single entities of triamterene and hydrochlorothiazide may show an increase in blood pressure or fluid retention. Similarly, it is also possible that the lesser hydrochlorothiazide bioavailability could lead to increased serum potassium levels. However, extensive clinical experience with 'Dyazide' suggests that these conditions have not been commonly observed in clinical practice. Angiotensin-converting enzyme (ACE) inhibitors can elevate serum potassium; use with caution with 'Dyazide'. Do periodic serum electrolyte determinations (particularly important in patients vomiting excessively or receiving parenteral fluids, and during concurrent use with amphotericin B or corticosteroids or corticotropin [ACTH]). Periodic BUN and serum creatinine determinations should be made, especially in the elderly, diabetics or those with suspected or confirmed renal insufficiency. Cumulative effects of the drug may develop in patients with impaired renal function. Thiazides should be used with caution in patients with impaired hepatic function. They can precipitate coma in patients with severe liver disease. Observe regularly for possible blood dyscrasias, liver damage, other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving triamterene, and leukopenia, thrombocytopenia, agranulocytosis, and aplastic and hemolytic anemia have been reported with thiazides. Thiazides may cause manifestation of latent diabetes mellitus. The effects of oral anticoagulants may be decreased when used concurrently with hydrochlorothiazide; dosage adjustments may be necessary. Clinically insignificant reductions in arterial responsiveness to norepinephrine have been reported. Thiazides have also been shown to increase the paralyzing effect of nondepolarizing muscle relaxants such as tubocurarine. Triamterene is a weak folic acid antagonist. Do periodic blood studies in cirrhotics with splenomegaly. Antihypertensive effects may be enhanced in post-sympathectomy patients. Use cautiously in surgical patients. Triamterene has been found in renal stones in association with the other usual calculus components. Therefore, 'Dyazide' should be used with caution in patients with histories of stone formation. A few occurrences of acute renal failure have been reported in patients on 'Dyazide' when treated with indomethacin. Therefore, caution is advised in administering nonsteroidal anti-inflammatory agents with 'Dyazide'. The following may occur: transient elevated BUN or creatinine or both, hyperchloremia and glycosuria (diabetic insulin requirements may be altered), hyperuricemia and gout, digitalis intoxication (in hypokalemia), decreasing alkali reserve with possible metabolic acidosis. 'Dyazide' interferes with fluorescent measurement of quinidine. Hypokalemia is uncommon with 'Dyazide', but should develop, corrective measures should be taken such as potassium supplementation or increased dietary intake of potassium-rich foods. Corrective measures should be instituted cautiously and serum potassium levels determined. Discontinue corrective measures and 'Dyazide' should laboratory values reveal elevated serum potassium. Chloride deficit may occur as well as dilutional hyponatremia. Concurrent use with chlorpropamide may increase the risk of severe hyponatremia. Serum PBI levels may decrease without signs of thyroid disturbance. Calcium excretion is decreased by thiazides. 'Dyazide' should be withdrawn before conducting tests for parathyroid function. Thiazides may additionally potentiate the action of other antihypertensive drugs. Diuretics reduce renal clearance of lithium and increase the risk of lithium toxicity.*

***Adverse Reactions:*** *Muscle cramps, weakness, dizziness, headache, dry mouth; anaphylaxis, rash, urticaria, photosensitivity, purpura, other dermatological conditions; nausea and vomiting, diarrhea, constipation, other gastrointestinal disturbances; postural hypotension (may be aggravated by alcohol, barbiturates, or narcotics). Necrotizing vasculitis, paresthesias, icterus, pancreatitis, xanthopsia and respiratory distress including pneumonitis and pulmonary edema, transient blurred vision, sialadenitis, and vertigo have occurred with thiazides alone. Triamterene has been found in renal stones in association with other usual calculus components. Rare incidents of acute interstitial nephritis have been reported. Impotence has been reported in a few patients on 'Dyazide', although a causal relationship has not been established.*

***Supplied:*** *'Dyazide' is supplied as a red and white capsule in bottles of 1000 capsules; Single Unit Packages (unit dose) of 100 (intended for institutional use only); in Patient-Pak™ unit-of-use bottles of 100.*

*BRS-DZ-L42*

*a product of*

**SK&F CO.**

*Carolina, P.R. 00630*

© SK&F Co., 1

JOURNAL OF THE ARIZONA MEDICAL ASSOCIATION

ARIZONA MEDICINE

JUNE 1987, VOL. XLIV, NO. 6

# Who's Really Caring For Our Patients?

Marshall B. Block, M.D.

After admitting a patient early one morning to the hospital, I was leaving the floor when a nurse said to me, "Don't worry, Dr. Block, we'll take good care of your patient." As I was walking toward the elevator I thought about that comment and thought that she really was correct without even knowing it. Not that she was going to take *good care* of my patient, but rather that she was going to *care* for my patient. Nurses are the ones who are actually caring for our patients.

As an example, Mrs. Jones is admitted to the hospital in the middle of the night with a chief complaint of shortness of breath and chest pain. She is admitted to the Intensive Care Unit after her vital signs are taken in the Emergency Room and she is examined by the Emergency Room physician. He in turn has called the attending physician who agrees that the acute nature of the patient's symptoms and a chest x-ray showing bilateral pleural effusions suggests the presence of congestive heart failure. The patient is brought by a nurse to the Intensive Care Unit. She is then admitted by the nursing staff of the Intensive Care Unit, who do all of the necessary chores and monitor the patient using telemetry until the attending physician arrives at 6:00 in the morning. He observes the patient's clinical signs and her response to the therapy that was instituted in the Emergency Room and writes additional orders for care during the rest of the day. He writes contingency orders so that if certain situations arise he is to be called for follow-up orders. He then leaves the floor either to see additional patients or return to his office for a busy day caring for patients. The nursing staff follows his orders and brings the patient her breakfast tray, then gives her insulin since she is a diabetic, and follows the intravenous fluid orders and other intravenous medications that have been prescribed. They bring her bedpan and they remove it and empty it. They check her vital signs three or four times during the morning, and present her with her luncheon tray. The attending physician, because of his concern for the unstable nature of her cardiovascular status, returns to see her at noon and writes additional orders based upon the results of the laboratory studies which were returned from early morning. In the afternoon, shifts change and a new nursing staff arrives and begins to review the patient's clinical status.

This sequence of events occurs three times a day while every one of our patients is hospitalized, either in the Intensive Care Unit or on the floors. As attending physicians we see the patient, usually in the morning but on occasion twice or even three times a day, depending upon the clinical status of the patient. The amount of time we spend with the patient is small compared to the time the patient is in the hospital every day. True, we write orders in the chart and review laboratory and radiological studies as they return

**(Continued on pg. 14)**

JOURNAL OF THE ARIZONA MEDICAL ASSOCIATION

ARIZONA MEDICINE

JUNE 1987, VOL. XLIV, NO. 6

*Arizona Medicine* is a socioeconomic and scientific journal published monthly by The Arizona Medical Association, Inc., 810 West Bethany Home Road, Phoenix, Arizona 85013, in conjunction with *The Western Journal of Medicine*. All views and opinions expressed in the articles published herein are the authors' and may or may not reflect those endorsed by The Arizona Medical Association.

(602) 246-8901 in Phoenix
1-800-482-3480 Statewide

Neil O. Ward, M.D.
*President*
Bruce E. Robinson
*Executive Vice President*
Misty Coumbe
*Assistant Executive Vice President*
Chic Older
*Assistant Executive Vice President*

Marshall B. Block, M.D.
*Editor*
Thomas J. Marks
*Manager of Publishing*
Susan Fuchs
*Communications Director*
Linda N. Brown
*Editorial Assistant*

Please notify publisher at least six weeks prior to change of address and include old and new addresses and a mailing label from most recent copy of *Arizona Medicine*. Include your new postal Zip Code number.

**IN THIS ISSUE . . .**


- Doctors Asked to Fight Seductive Killer
- Physicians in the News
- Research and Teaching In a College of Medicine *University of Arizona*
- Extended Phone Hours Make Marketing Sense *George S. Conomikes*
- New Active Members
- Medical Facts

## From Our President

Neil O. Ward, M.D.

# Can We Mend The Medicare Mess?

Over twenty percent of ArMA's active members responded to our inquiries about their experience with new Medicare rules and regulations. Only one percent said new rules had a positive effect on patient care. Thirty-four percent indicated no effect on their practices with the following generic explanations appended to several of the survey responses: (a) "No effect because I don't treat Medicare patients" or (b) "No effect because my office absorbed the cost of care denied or undercompensated." Fully *sixty-five percent* of ArMA respondents said the new Medicare rules and regulations *adversely affected* the quantity and/or quality of their patient care!

When asked for actual numbers, the responding physicians estimated 15,000 Arizona patients have been adversely affected by new Medicare rules. This can be extrapolated to cover the entire active physician population of the state to *conservatively* estimate that more than 100,000 Medicare patients have been denied the best care available because of Federal incentives to limit medical services!

Medicare programs have assured the elderly and the disabled high quality, mainstream, medical care. The nation's budget deficits have made Medicare a prime target for cost containment. Short term cost containment "solutions" including the 1973 physician fee freeze and the hospital DRGs have not reduced Medicare cost. Nor are they likely to do so with an aging population, better and more expensive technology to treat senior citizens who consume four times the health care resources of those under age 65, and a DRG system that motivates "quicker and sicker" discharges of the elderly into the community.

This is a complex problem that can be solved cooperatively by informed physicians, patients and our political representatives.

1.) Physicians must constrain colleagues who would provide unnecessary medical services. This can be accomplished through educational, ethical, economic and due process peer review incentives. We currently don't know the "right rate" of medical care. Arizona physicians must study the growing mountain of computerized data available to hospitals, the PRO, the Department of Health Services and third-party payors. We plan to do that at ArMA through ArMAP (Arizona Medical Assessment Programs).

The percentage of physicians accepting Medicare assignment can increase even while "participation" in Medicare declines. The AMA

**(Continued on pg. 14)**

# MICA

## SYNONYMOUS WITH QUALITY MEDICAL MALPRACTICE INSURANCE FOR THE PREFERRED ARIZONA PHYSICIAN

For more facts, please call the MICA Underwriting Department (602) 956-5276
or toll free (800) 352-0402

MICA MICA MICA MICA MICA

MUTUAL INSURANCE COMPANY OF ARIZONA Sponsored by: Arizona Medical Association
Arizona Osteopathic Medical Association

# Doctors Asked to Fight Seductive Killer

The #1 one killer of preschool kids in Arizona sparkles with sunlit, seductive glamour, luring toddlers into its lethal grasp — but state health officials say that with the help of alert adults, the killer is conquerable.

The killer, of course, is water .... water in canals, lakes, rivers and decorative ponds, but mostly water in backyard swimming pools. And Arizona's physicians are being asked to man the front lines in the battle to educate and raise the consciousness levels of Arizona's adults, particularly the parents of children at risk.

"People don't tend to view their pool as the #1 hazard to their children's lives," one expert observes, "but we need to urge them to think of their pool as being as deadly and dangerous as the traffic in the street out front."

In fact, drowning kills more children under age 5 than any other factor, surpassing both traffic accidents and illness as the primary cause of death of children aged one through four. And in Arizona, it's not just a summer hazard; it's a 12-month-a-year hazard lurking in our lives, often on our property, threatening our children.

The tragedy, officials say, is that drowning is preventable. Physicians are being urged to share some basic information with patients who are parents of small children.

This is the state's third annual "Children Aren't Waterproof" drowning campaign. Colorful, attractive and easy-to-read brochures are available, free of charge and in quantity, to physicians for distribution to patients. Brochures may be obtained by contacting the Community Health Education Office at Tucson Medical Center, (602) 327-5461.

According to Barbara Smith, M.D., Tucson pediatrician, and Chairman of the Accident and Injury Prevention Committee of the Arizona Chapter of the American Academy of Pediatrics, the biggest challenge of the ongoing educational campaign is to make people, especially parents, aware that drowning is a major health problem. "People just don't realize

*Photo by Susan Fuchs*

**St. Joseph's Hospital water safety spokesman Oliver Otter, complete with goggles and bathing suit, shares swimming rules with pupils at the Montessori Day School in Phoenix as the state's third annual "Children Aren't Waterproof" drowning prevention campaign begins. Physicians are asked to stress the need for water safety to patients who are parents.**

how serious this is," Dr. Smith said. "They worry about their kids playing in the street and the danger of traffic, but they need to realize the backyard can be just as dangerous."

Supervision is the key to protecting small children, Dr. Smith said. If physicians only get one bit of information across to their patients who are parents of small children, it is that toddlers need to be watched every moment when they have access to the backyard pool.

"The biggest cause of drowning incidents is parental distraction," she said. "The phone rings or something else happens which takes the parent's attention away from the child at the pool, even for just a moment. And children can move quickly. It only takes a moment for a child to get in serious trouble."

Physicians also need to let their patients know that small children do not necessarily make noise when they fall in the pool. Toddler drownings are usually very silent incidents.

"Tiny children don't make much of a splash, and they don't have the muscles to hold their heads up and yell for help. Parents think they'll hear something if their child falls in, but that's not true," she said.

"Barriers are the next most important protection after supervision," Dr. Smith said. "Physicians should point out to parents that locked gates do not substitute for supervision, but they can give parents a couple of moments of leeway if the child gets out of sight for a moment."

"Gates should have a self-closing and automatic locking mechanism, and fence uprights should be five feet tall and no more than three and three-quarter inches apart," she said.

"City codes sometimes call for a maximum of five inches between the bars of fences," she said, "but we've done demonstrations showing a toddler squeezing through a five-inch wide space."

"Parents especially should be warned not to self-defeat their protective systems," she said. "We see too many cases of tragedy that happened because a self-locking gate was propped open, or because the latch got rusty and didn't close properly."

"CPR and a portable telephone near the pool can save lives if tragedy does occur," she added. "If parents have a pool, they should be currently trained in CPR; when CPR is performed immediately, any child will have a better chance of survival than if it has to wait for emergency personnel to arrive." The telephone should have the emergency rescue phone number and the address of the home attached, so visiting relatives or baby sitters will know where to call for help and can tell rescuers exactly where to come.

"Finally," Dr. Smith said, "physicians should make sure parents understand that tiny children cannot be 'drownproofed'."

"Swimming lessons are wonderful as far as having a good time, one on one, where your toddler is concerned," she said, "but swimming lessons cannot be relied upon to give a tiny child the ability to save himself if he falls in the pool. Parents should never let themselves get complacent. They must understand that children must be watched around water, and physicians are in a position to get that fact across to them." ■

**MEDI-LOGS are still available.**

**Contact The Arizona Medical Association**

810 W. Bethany Home Rd.
Phoenix, Arizona 85013
246-8901

# *Introducing* **POMS**

**The *"Professional Office Management System"* for Physicians!**
**Your most complete "Solution" on the market today.**

***Proven Reliability!*** **Designed by Doctors, for Doctors along with an 8 year performance record!**

## — FEATURES —

• User Friendly • On-Site Training • Local Support •
• Appointment Scheduling • On Line Claim Processing •
• Patient/Clinical/Procedure Histories • Patient Recalls •
• A/R Management & Billing • Word Processing •
• Over 20 Reports Tailored To *Your* Practice •

## — PLUS —

• Lease Option Available • Satisfaction Guaranteed •

## — OPTIONS —

• Electronic Claims Submission •
*On Line Access to*
*The National Library of Medicine's "Medline"*

To see the **"POMS"** System in use:

***Please Call***

**Local Dealer**

cims
Computer Information Management Systems
Campbell Executive Offices
3503 N. Campbell, Suite 300
Tucson, AZ 85719
(602) 326-0915

or

**Distributor**

DEPENDABLE DATA SYSTEMS
220 W. Calle De Las Tiendas
Green Valley, AZ 8571[illegible]
(602) 625-919[illegible]

**STATE OF THE ART** **RELIABLE** **LOCALLY SUPPORTED**
**EXPANDABLE** **EASY TO USE**

# Physicians in the News

Ronald P. Spark, M.D.

## UA Alumni Honor Two Physicians

The University of Arizona Alumni Association has been recognizing recipients of the Distinguished Citizen Award for over 40 years. It selects its honorees from nominations submitted by the various Colleges of the University.

Arthur V. Dudley, Jr., M.D., and Ronald P. Spark, M.D., were both nominated by the University of Arizona College of Medicine and its Dean, Louis J. Kettel, M.D.

The awards were presented during graduation ceremonies for the College of Medicine on May 15, 1987. During the recognition ceremonies, Dr. Dudley and Dr. Spark were each presented with a plaque honoring their contributions to medicine and the community and a citation summarizing their major achievements.

Photo by Sister Cecilia Joseph Wight, C.S.J.

Arthur V. Dudley, Jr., M.D.

The University of Arizona's Alumni Association has awarded its Distinguished Citizen Award to Tucson Medical Center pathologist **Ronald P. Spark, M.D.**, in recognition of his leadership in public health education.

"Dr. Spark has been a leader in the effort to reach out to the public with information they need regarding their health," said Louis J. Kettel, M.D., Dean of the University of Arizona College of Medicine. "He is perhaps the most media-conscious physician in the Tucson area, an indefatigable spirit in the medical and Tucson public service communities."

Co-founder and moderator of the Pima County Medical Society weekly radio program and cable TV series, both of which are called "Prescription for Health," Dr.

**(Continued on pg. 8)**

Former Arizona Medical Association (ArMA) President **Arthur V. Dudley, Jr., M.D.**, has been awarded the University of Arizona Alumni Association's Distinguished Citizen Award in recognition of his years of service to the medical community, the University of College of Medicine and its student body.

"Dr. Dudley has been an extremely strong supporter of the College of Medicine, as well as an active participant in community activities," said Louis J. Kettel, Dean of the University of Arizona College of Medicine.

"He has always been a friend of medical students," Dean Kettel added, "and shows great concern about the mechanisms available for them to fund their education."

In 1977, the Arizona Legisla-

**(Continued on pg. 8)**

## Arthur V. Dudley, M.D.

*(Continued from pg. 7)*

ture passed a bill establishing the Arizona Medical Student Loan Board, which provides $6,000 loans each year for students who are willing to commit themselves to serving underserved areas in the State of Arizona. Dr. Dudley was active in lobbying for the success of this measure in the legislature and was among the first appointees to serve on the Board, which elected him its first chairman.

Dr. Dudley also worked within ArMA to further provide for the student financial aid he so strongly supports, and he helped establish a scholarship fund through ArMA, utilizing interest from short-term investments. Known as the Association's Benevolent and Loan Fund Committee scholarship program for medical students, Dr. Dudley serves as its chairman.

A member of the Pima County Medical Society, Dr. Dudley has staff privileges at St. Mary's Hospital in Tucson and at the Tucson Medical Center. A teaching associate in family practice at the U. of A. College of Medicine, he is known as a friend of the student body.

A member of ArMA since 1974, Dr. Dudley served as ArMA Treasurer from 1961 through 1966 and was elected ArMA Vice President for 1966-67, President-Elect for 1967-68 and President for 1968-69.

Dr. Dudley has also served on ArMA's Budget and Finance Committee, Insurance and Industrial Relations Committee, Building and Long Range Planning Committee, and Ad Hoc Committee on Emergency Room Service.

Dr. Dudley represented Arizona as an Alternate Delegate to the American Medical Association from 1971 through 1976 and as a Delegate to the AMA from 1977 through 1980.

A native of California, he received his undergraduate college education at the Universities of California, Missouri and Minnesota. In 1949, he earned his medical degree at the University of Cincinnati, Ohio. Board Certified in Family Practice, he is a member of the Arizona Chapter of the American Academy of General Practice.

He came to Tucson and was licensed to practice medicine in Arizona in 1954 after serving four years as a physician in the U.S. Air Force.

## Ronald P. Spark, M.D.

*(Continued from pg. 7)*

Spark has been active in providing the public and the media with information about the health-related issues.

Dr. Spark was even more active in the recent political referendum in Sierra Vista, which could have eliminated the last inexpensive source of animals for medical research at the University.

Dr. Spark's public education activity has been recognized by the Tucson Press Club which gave him its Orchid award and by the National Association of Physician Broadcasters which named him one of its charter members. The Arizona Division of the American Cancer Society gave him its Distinguished Service Award in 1985 for his public service, particularly his anti-smoking educational efforts.

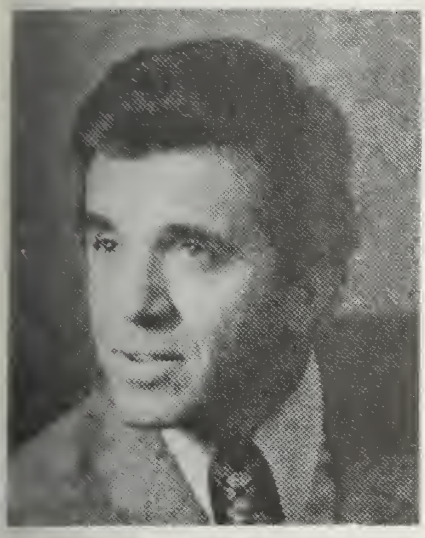
President of the Pima County Medical Society in 1985, Dr. Spark has held virtually every elective office in the Society. A member of the Arizona Medical Association House of Delegates since 1979, he has served on ArMA's Health Manpower Committee since 1978. An Executive Board Member of the Arizona Society of Pathologists since 1977, Dr. Spark served as their president in 1980.

Dr. Spark serves as consultant pathologist to Kino Community Hospital, St. Joseph's Hospital in Nogales, Benson Hospital, Cochise County Hospital in Douglas, Northern Cochise Hospital in Wilcox, and at the Indian Health Service Hospital in Sells. He also is an associate in pathology, an unpaid position, in the U. of A. College of Medicine and has served as a lecturer at the College.

A native of Philadelphia, Dr. Spark earned his B.A. at Johns Hopkins University, Baltimore, Maryland, and was graduated from Temple University Medical School in 1967. He was a clinical clerk in pathology at the Armed Forces Institute of Pathology in Washington, D.C., interned at the Graduate Hospital of the University of Pennsylvania, and served his residence in clinical and anatomic pathology at the Pennsylvania Hospital in Philadelphia. He was Board Certified in Anatomic and Clinical Pathology in 1972.

He came to Tucson and was licensed to practice medicine in Arizona in 1974 after serving two years as staff pathologist and chief of the chemistry section at Fitzsimons Army Medical Center.

## More Physicians in the News



Thomas Foerster, MD.

### Orthopedist Awarded Medal

Orthopedic surgeon **Thomas Foerster, M.D.**, chairman of the Arizona Medical Association's Sports Medicine Symposium subcommittee, was recently awarded the Clarence Salsbury Medal by the Maricopa County Medical Society.

The medal is awarded annually to a physician who displays selfless, dedicated service to his or her fellow man. According to the Medical Society Journal, Foerster was chosen "for his dedicated pursuit of the advancement of medical science through the design of the basic athletic sports injury care program, which is designed to recognize and prevent acute injury to athletes in this country and throughout the world."

Foerster has an extensive history in general orthopedics and sports medicine. He is the Arizona consultant for the Milwaukee Brewer's minor league teams during spring training and is co-founder of BASIC, the first-aid course designed for the sport field, for which he won the medal.

### Talk to Us!

Have you received special recognition or an award recently from your specialty society or a community organization? Do you know of a colleague who has similarly been honored for medical or community contributions?

If so, please let us know. Call Arizona Medicine at 246-8901 in Phoenix, or 1-800-482-3480 toll-free statewide. We'd love to share the good news with medical professionals throughout Arizona.

# Ophthalmologist Wins Research Film Award

A highly specialized movie, shot from the inside of the eye looking out, reversed ophthalmological theory about the quality of the zonular basket and won the equivalent of an eye surgeon's "Oscar" for ophthalmologist **Samuel L. Pallin, M.D., F.A.C.S.**

The 10-minute videotape, titled "The Amazing Zonular Basket," demonstrated that the zonule of the lens of the eye, previously thought to be very fragile, is in fact extremely tough and resilient as related to cataract surgery.

The film was produced in March in cooperation with IOLAB Corporation in California during cataract surgery by Dr. Pallin, assisted by charge nurse Deb Smaltz, R.N., B.S. The movie production used the Miyake technique of photography which actually films from the inside of the eye outward. The process provided the surgeons with a new understanding of ocular anatomy.

Shown at the Annual Meeting of the American Society of Cataract and Refractive Surgery in Orlando, Florida, in early April, the videotape won first place in the category Cataract Surgery/ Anatomical Research.

Samuel L. Pallin, M.D.

During the meeting, Dr. Pallin presented a free paper titled "The Endophthalmitis Detective" about post-operative infection and presided over a two-hour course on the same subject for surgeons and nurses.

Dr. Pallin, medical director of the Lear Eye Clinics in Sun City and Scottsdale, is a 1968 graduate of the College of Medicine of the State University of New York in Brooklyn, New York. He has practiced in Arizona since January, 1975, and is Board Certified in ophthalmology.

# Research and Teaching in a College of Medicine

The missions of the College of Medicine include teaching, research and service. The research and teaching missions are sometimes in conflict because of limitations of resources and time. Partly because of these conflicts, there is a myth popular in some circles that good researchers make bad teachers. This myth is not true. Of course, the converse is also not true, that all good researchers are good teachers. What is true is that involvement in research can make any faculty member a better teacher. Indeed, a well-known College of Medicine investigator recently stated publically that he really preferred teaching but did his research so that he had something to teach!

The main reason that research improves teaching is motivation. It is involvement in, and commitment to, research that provides the motivation necessary to spend long hours to examine carefully, to digest and understand, every shred written or said about a particular topic. Research inspires extra effort because at national meetings or in research articles authored for national and international journals, the researcher simply cannot afford to be poorly informed, to lag behind in understanding new concepts, or to have missed recent advances in a distant laboratory. Such lapses are glaringly apparent and, in the scientific tradition of detailed peer review, are immediately and pointedly brought to the researcher's attention. Such kicks in the shin are embarrassing at best and devastating to the researcher's reputation and career at worst. Investment of the time necessary to keep pace with rapid advances in medicine requires strong motivation that commitment to research can provide.

The active researcher is afforded many unique opportunities to gain early information about new facts or concepts. The researcher may serve as a manuscript reviewer, or even as an editor, and sees the results of research in many months before it is published. The researcher may serve on government or health agency review panels and sees the structure, design and intent of experiments even before the research takes place. The researcher is likely to participate in national and international scientific meetings, conferences and symposia where new information and concepts are discussed and analyzed in depth by experts. The researcher is often a more critical reader of journal articles because of great familiarity with experimental design and experimental methodology.

The scientific method, which defines research and sets it apart from mere observation, requires an organized, methodical approach that becomes a way of thinking. The organized, logical approach to knowledge spills over into teaching. Students learn organized material faster and better than disorganized, randomly presented material, whether it is presentation of a case or a lecture on oncogenes. In addition, the researcher's enthusiasm about new discoveries is likely to carry a sense of excitement into the classroom or conference room where the students can be infected by it. This concept is so important that medical college accreditation demands evidence of a learning environment steeped in the spirit of inquiry.

The research environment has a major favorable impact on education by attracting government and industrial financial support for enlarged libraries and computer facilities, greater concentration of experts in esoteric subjects, access to the latest technology, experimental drugs and procedures, and specialized facilities for teaching medical and graduate students, from sophisticated imaging techniques to peptide and nucleotide synthesis.

Teaching, has itself, a positive impact on research. Teaching forces the researcher to step back occasionally from specific experiments and take a broader view of the specific medical field, where it

is, where it has been, and where it is going. This broad view helps put the researcher's immediate interests into perspective, and leads to new ideas and new directions of research. Moreover, the researcher is more likely to see logical flaws in the research fabric if required to view the whole cloth from time to time for purposes of teaching. In addition, bright, perceptive students often themselves pose penetrating questions that cause the researcher to reevaluate even cherished concepts. Researchers and teachers share in common a love of scholarship and respect for truth. It is through research that new truths are discovered and old truths reaffirmed or disproved and discarded. Medical science is dynamic and has never moved faster than at the present. Investment of the time and energy necessary for keeping pace with rapid advances and new truths in medicine requires strong motivation. Commitment to research is a powerful motivator. ■

**Thomas F. Burks, Ph.D.**
**Professor and Head**
**Department of Pharmacology**

**Louis J. Kettel, M.D.**
**Dean**
**College of Medicine**
**University of Arizona**

# Extended Phone Hours Make Marketing Sense

Do you want your practice to increase its patient volume? Do you want to attract new patients to your practice as well as keep your established patients satisfied? One of the best ways to do this is to make yourself more available to patients and referring physicians.

Availability means phone availability as well as office hours. For example, a physician at one of our Marketing Workshops in Oregon told us that simply by having the phone answered at his practice during lunch hours (a practice that they had not done for a number of years) he witnessed a measurable increase in new patient volume plus complimentary comments from established patients. As a matter of fact, the physician was so encouraged by these results that he even decided to see patients during lunch hours. The net result of these decisions was an increase in business significant enough to counteract prior patient erosion.

You need to recognize that patients are finding it increasingly difficult to reach your practice. One of the biggest demographic changes that has taken place in the United States has been largely ignored by many practitioners — and this has led to increasing frustration on the part of your patient base. The phenomenon is that, today, twice as many married women are full-time employees than was the case 25 and 30 years ago. Today approximately 65% of all married women are full-time employees. Fifty percent of women with children under the

age of 5 are also full-time employees. Twenty-five years ago, the statistics for married women as employees were exactly half of the ones just quoted.

How does this affect you? It is increasingly difficult for working women (as well as working men) to reach your offices during their working hours. Many work in offices and department stores where outgoing calls are restricted. So if we look at your average working patients, the question is: when can they contact your office? They have to try to do this before they go to work (which means before their traditional 9:00 a.m. or 8:30 a.m starting time), or they may try to call you during their lunch hour if that is convenient for them.

Let's role-play this: Mrs. Patient gets up in the morning and is not feeling well and wants to call your office. She calls, and gets an answer from your answering service that the office is closed and will open at 9:00 a. m. If Mrs. Patient starts working at 9:00 a. m. and is unable to call from work, what is she expected to do? The answer is to find somebody who will answer the phone or someone that is available. This has been one of the big growth areas for your competitive "urgent-care centers." They do a booming business in the morning hours preceding working hours. We assume the major reason for this is that people are not able to reach your office. If Mrs. Patient could actually reach someone in your office, then an appointment

**(Continued on pg. 12)**

## Extended Phone Hours

*(Continued from pg. 11)*

could be made or at least answers to her medical problems could be received.

In other instances, Mrs. Patient will try to reach your office during lunch hours. What if your office is "closed" for lunch? Again we have an added bit of irritation based on your non-accessibility.

Availability means phone availability, almost as much as office hours availability. We are recommending that offices consider the following extension of their availability to patients.

First, we feel that most medical offices should have someone at the office answering the telephone approximately one hour prior to normal working hours in your community. In other words if most people in your community start working at 8:30 a.m., we suggest someone in your office be answering the telephone at 7:30 a.m. (one hour earlier): This does not mean that you are open for business, i.e., available for patient visits. (This is no different from an office answering the phone at 9:00 a.m. for a physician that is not in the office until 1:00 p.m.) Being available does not require anything more than one employee coming to the office earlier than usual (and probably having the opportunity to leave earlier in the day).

If you are not answering your phone before traditional starting hours (whether this be 8:00 a.m. or 8:30 a.m. or 9:00 a.m. in your community) the patient runs into one other stumbling block. The hour preceding normal starting hours for most medical offices is also the busiest hour for answering services. Our experience with answering services is that their busiest times are the hour preceding usual starting times for medical offices in their communities. So, that important patient calling your office may have to let the phone ring a dozen or more times before the answering service can get to it — due to their peak load problem. New patients, the backbone of your marketing efforts, won't bother to wait.

The same problem occurs if your office is "closed" for lunch. We have been to medical offices with 8 and 15 employees that are closed for lunch. This is just another slap in the face to the patient who is trying to reach you during "normal" business hours. We know very few businesses that are closed for lunch except medical businesses. Again, this may mean that the working hours of your employees may have to be adjusted. In our consulting work, we have been to many two-employee offices where both employees were "off" for lunch. By simply staggering their lunch hours, these practices were able to achieve improved phone coverage for their patients.

Other phone availability ideas: many practices close for four days over the Thanksgiving weekend. We see nothing wrong with the practice taking a vacation for four days. It may provide a much-needed break after a busy September, October and early November. However, smart practitioners do the folllowing: one employee goes to the office on the Friday after Thanksgiving to cover incoming phone traffic. These physicians feel the practice should not be on answering service for four sequential days (Thursday, Friday, Saturday, and Sunday). This makes good business sense. Even a good answering service is not a substitute for a competent employee representing the practice itself. Some of the practices that have a person covering the telephone on the Friday following Thanksgiving give that employee a bonus day off during the Christmas holidays.

Again, some practices may observe religious holidays that are not uniform for the community. We recommend that perhaps on such religious or other holidays consideration be given to having an employee at the office managing the telephone. By this we don't mean Christmas or New Year's but we do mean other holidays, such as Washington's birthday, Good Friday, Columbus Day, Election Day, Veteran's Day, etc.

Like AT&T, by better phone coverage, you may be able to "reach out and touch someome."

■ **George S. Conomikes, President Conomikes Associates, Inc.**

**ARIZONA PHYSICIANS' DIRECTORY**

Announcing a
Practice?
Relocating?
New Physician?

Block space is available in *Arizona Medicine* for advising member physicians.

Two-month minimum. Payment must accompany order.

Members — $20 per month
Nonmembers — $30 per month

# The Simplicity of Modern Medicine

Eliminate the problems and paperwork of filling out and filing insurance claims for Medicare, Blue Cross and all other types of medical insurance with our universal, card-based system.

Patient cards, coupled with an easy-to-operate transmission device in your office, assure that medical claims are filed quickly, accurately and electronically from a standard telephone line in your office.

Most importantly, you'll be paid quickly...in an average of 7 to 18 days (or less) and there is no charge for the transmission device, its installation, or your medical assistant's training. And, there's no long-term contractual obligation.

Fees for the service are transaction-based and are charged only when you use the system.

For more information on this innovative new service sponsored by the American Medical Association, contact your local medical society or call us at

(602) 246-8901
or 1-800-482-3480

Why wait?
Call today.

*For further information, write or call*
*Medical Payment Systems, Inc., Phoenix. AZ 85013*
*602-246-8901*

# Use of Automatic External Defibrillators

Use of automatic external defibrillators (AEDs) by emergency medical personnel may facilitate treatment for more victims of heart attacks, according to a study reported recently in *JAMA*. The study found that automatic devices required less training for proper use and that they delivered shock to the heart one minute faster than standard defibrillators.

Richard O. Cummins, M.D., M.P.H., M.S.C., of the University of Washington, Seattle, and colleagues, compared the effectiveness of both kinds of defibrillators used by emergency medical technicians (EMTs) in treating 321 patients with cardiac arrest. In their study, 116 patients were treated with AEDs, and 158 were treated with standard defibrillators (an additional 47 were treated by EMTs using the standard defibrillator even though they were assigned to use the AED).

Hospital admission and discharge rates of patients were comparable regardless of the type of device used. "The only significant difference observed was in the time from power on to first shock: 1.1 minutes average AUTO group and 2.0 minutes average standard group," the researchers say.

"Automatic external defibrillators appear to have advantages over standard defibrillators in training, skill retention, and faster operation," the report adds, noting that AEDs can make early defibrillation available for a much larger portion of the population.

**(Continued on pg. 15)**

## Editor's Message

*(Continued from pg. 1)*

to the chart on behalf of the patient, but our actual expenditure of time with the patient is not great, and the amount of "caring" that we do is small.

Watching many attendings berate nurses (I've been guilty of this myself) leads me to suggest that we really are off base. We need to be sure that the nursing staff at every hospital is carefully selected and given responsibilities commensurate with their abilities. Furthermore, we should have compassion and understanding for the difficult task they must undertake on a daily basis caring for our sick patients. I believe we have lost sight of the role that the nurse plays in the overall scheme of things and they should be given a greater attention and reward for their efforts. If it were not for the nursing staff at every hospital, our patients would not get the care we are prescribing. It wouldn't hurt to say, "Thank you, for caring for my patient," when you see a good job being done by the nursing staff. They need our support and we need theirs. ■

**Marshall B. Block, M.D., Editor**

## President's Message

*(Continued from pg. 2)*

and ArMA urge physicians to consider each patient's financial needs when setting charges and to accept Medicare assignment, reduce fees, or charge no fee at all in cases of true financial hardship.

Physician reimbursement must be more predictable and less inequitable. It is past time we had a resource-based relative value scale based on actual costs including factors such as the time required to provide a service, the complexity of the service, the training, equipment and overhead expense required to provide the service and the risk involved. Congress is working "at" it.

2.) Patients must be aware of cost and co-pay more when appropriate. When the Medicare system is threatened financially, there is no justification for subsidized care to those who are well-to-do. A "means test" may not be popular but it's good for the system. Medical research for better treatment in the near future and the education of new physicians are at risk in the current system that fails to realistically reimburse for medically indicated care.

Patients must be reminded that in our pluralistic society they will not be well-served by being forced into a particular delivery system based on the federal government's administrative convenience or perceived cost savings.

3.) The government must be persuaded to stop rearranging the deck chairs and do what's necessary to save sinking Medicare with sound fiscal policy (see AMA: *Proposal for Financing Health Care of the Elderly*, Report of the Board of Trustees to the House of Delegates Annual Meeting, Chicago, Illinois, June 1986.) It is long overdue!

Remember, *we* are the government and your patients are voters, too. Lobby them. If, as a physician, you perceive politics to be beneath you — reconsider Rudolf Virchow's observation that "medicine is in essence a social science and politics is nothing more than medicine on a larger scale."

Expand your practice a little! ■

**Neil O. Ward, M.D., President**

## AMA Slates Conference on Impaired Physicians

The American Medical Association will host a national conference on impaired physicians and other health professionals October 8-11, 1987, at the Drake Hotel in Chicago.

This is the eighth in a series of conferences sponsored by the AMA since the release of its landmark report 15 years ago entitled, "The Sick Doctor: Impairment by Psychiatric Illness, Including Alcoholism and Drug Dependence." The focus will be on the need for increased collaborative efforts among the health professions in educating not only themselves but also state licensure boards and medical educators.

To further emphasize the collaborative need, the conference is being co-sponsored by five other professional associations: The American Dental Association, American Nurses Association, American Pharmaceutical Association, American Podiatric Medical Association and American Veterinary Medical Association.

Persons wishing registration or program information should contact Janice Robertson at 312/645-5079.

### Defibrillators

*(Continued from pg. 14)*

The automatic devices take responsibility for rhythm identification away from prehospital rescuers, which can be beneficial especially in rural areas, where volunteers are trained to respond to emergencies. The researchers did encounter reluctance by some EMTs to use the new devices, especially those who had been previously trained with the standard devices and had been using them for more than eight years.

## Thymic Tissue Transplants in AIDS

Thymic tissue transplants, in combination with antiviral drugs, may offer a means of immune system reconstitution in AIDS patients, suggests a study in the March *Archives of Internal Medicine*. John M. Dwyer, PhD., M.B., B.S., now of the University of New South Wales, Kensington, Australia, and colleagues transplanted tissue from the immune-regulating thymus gland into 15 AIDS patients. The study says the procedure seemed to prompt partial, though selective and transient repopulation of the circulating T-cell pool in eight patients. In addition, the number of T8, but not T4, cells increased in eight patients a few weeks post-transplant; this was associated with some clinical improvement. "Thymic tissue transplantation as a single therapeutic maneuver is unlikely to reconstitute the immune system of patients with AIDS, but the potential of the approach, used in combination with agents that block replication of (the AIDS virus), deserves further study," the report says.

## Transfusion May Lower Cancer Survival

Blood transfusions may negatively affect survival for some cancer patients, a study in the March *Archives of Otolaryngology-Head and Neck Surgery* suggests. Jonas T. Johnson, M.D., of the University of Pittsburgh School of Medicine, and colleagues studied 179 patients who underwent surgical treatment for advanced squamous cell cancer of the head and neck, correlating treatment outcome with transfusions. Seventy-three percent of patients not needing a transfusion survived three years free of disease, the study says, compared with 47 percent of patients receiving three or four units of transfused blood, while 40 percent of patients receiving five units or more survived two years free of disease. "Blood transfusion may be detrimental to the management of patients with malignant neoplasms," the study concludes. "The mechanisms through which blood transfusion affects malignant neoplasms are unknown."

## Biochemical Factors in Arsonists

Poor control of impulsive, violent behavior, like arson, is associated with certain biochemical indicators; specifically, low levels of the key neurotransmitter serotonin and a hypoglycemic tendency, a study in the March *Archives of General Psychiatry* finds. Matti Virkkunen, M.D., of the University of Helsinki, Finland, and colleagues studied cerebrospinal fluid for an index of serotonin levels in 20 arsonists, 20 habitually violent offenders and 10 healthy people. Concentrations of this chemical indicator, called 5-HIAA, were significantly lower in the arsonists than in the others. In addition, the severity of repeated fire-setting behavior correlated with a measure of hypoglycemic tendency in the arsonists. The study suggests low serotonin, previously suspected in violence, may predispose for the low blood sugar levels, suspected in poor control of impulsive behavior.

# Designer Drugs "Eve" and "Ecstasy" Linked to Deaths

A recent article in *JAMA* reports on five deaths associated with the use of two controversial designer drugs that are chemical cousins of methamphetamine, or "speed"—MDEA, popularly known as "Eve," and MDMA, known as "Ecstasy."

In three cases, the drugs may have contributed to death by inducing heart arrhythmias in individuals with underlying natural disease, conclude Graeme P. Dowling, M.D., now of the Universities of Calgary and Alberta, Canada, and colleagues at the University of Texas Health Science Center, Dallas, and Southwestern Institute of Forensic Science, Dallas. In another patient, MDMA use preceded an episode of accidental death, the study says, while in the fifth case, MDMA "was the immediate cause of death," also arrhythmia-related.

"Death as a consequence of the use of these drugs appears to be rare, but it does occur; this outcome may be more common in individuals with underlying cardiac disease . . . It is hoped that the reporting of these cases will inaugurate a search for more objective information about MDMA and MDEA," the study says.

MDMA has been a popular recreational drug at least since the early 1980s. Also used by some psychiatrists as an adjunct to therapy, it is said to be "a pleasant way to get in touch with oneself," say the researchers, causing euphoria and enhanced sociability. It was available legally until July 1, 1985, when federal drug officials, citing its abuse potential and possible neurotoxic effects, ordered MDMA classified as a controlled substance.

While MDMA is still available on the illicit drug market, MDEA has appeared as a non-controllled substitute. MDEA is reported to have milder but similar effects to MDMA, the study reports. Both drugs are structurally similar to MDA, which has been shown to selectively damage nerve terminals in rats.

The five cases in which MDMA or MDEA was thought to have caused or contributed to death were seen over a nine-month period in the Dallas area. The victims included four men and one woman and ranged in age from 18 to 32 years.

In one case, a 22-year-old man apparently fell to his death after climbing a utility tower and coming into contact with a high-voltage power line. The man had ingested an unknown quantity of MDMA the previous evening, the report says.

In two other cases, involving a 25-year-old man found to have had MDEA in his system and a 21-year-old man who had ingested MDMA, the victims had underlying heart problems, the researchers report. "Although their cardiovascular effects are unknown, MDMA and MDEA may well have actions similar to their parent amphetamines, including increased cardiac output, hypertension and induction of arrhythmias." These cases are similar to an MDMA-related death reported in the popular press, the study notes. In another case, it says, MDEA use was associated with the sudden death of a 32-year-old man who had asthma, and "one cannot rule out the possibility that MDEA potentiated a cardiac arrhythmia in this individual whose cardiopulmonary function was already impaired."

The final case involved an 18-year-old woman who was healthy prior to her death, which followed ingestion of a small amount of MDMA and alcohol. She suffered a cardiac arrhythmia and could not be resuscitated, the researchers say.

"Unfortunately, these five cases do little to resolve the present controversy as to abuse potential and dangers of MDMA and MDEA vs. the possible therapeutic usefullness of MDMA in psychotherapy," the study concludes. "Deaths directly and indirectly related to the use of MDMA and MDEA do occur; however, they appear to be rare at this time. It would appear the preexisting cardiac disease may be one factor that predisposes individuals to sudden death when using these drugs."

# AMA Council Recommends Smoke Detectors

Smoke detectors represent one of the least expensive and most effective means of providing early warning of fires, and may substantially reduce personal injury and death, according to a report from the AMA Council on Scientific Affairs, published recently in *JAMA*. The chance of death in homes without detectors is 2.5 times higher than those with the devices, the report adds.

While there is insufficient evidence to gauge the reliability of residential sprinkler systems, industrial/commercial systems show an outstanding record, observes the report, which was adopted at the June 1986 annual meeting of the AMA House of Delegates.

**(Continued on pg. 17)**

**Smoke Detectors**
*(Continued from pg. 16)*

Fire is the second leading cause of accidental deaths in the home, after falls; from 1977 to 1983, civilian deaths from fire averaged almost 7,000 per year. "Careless smoking caused the most fatalities (23.1 percent in 1983)," the report notes, "these incidents usually occurred at night, and the smoker often had been drinking. Cooking was blamed for the largest proportion of the fire injuries (15.6 percent), while arson accounted for the largest economic loss."

A major obstacle to implementing detectors in all homes is economic, the report adds. Many families cannot afford the cost of $10 to $50. With sprinklers, additional obstacles include problems of installation, and fear of possible water damage. However, sprinklers may be more helpful than smoke detectors in protecting young children and elderly or handicapped persons who have limited mobility.

The Council recommends that the AMA help educate the public regarding fire prevention and fire safety; encourage legislation requiring smoke detectors and encouraging sprinklers in all new residential and commercial buildings, and requiring both in high-rise buildings; encourage taxing bodies and insurance carriers to grant monetary concessions as inducements to property owners to install these devices; encourage manufacturers to develop increasingly effective and less costly products; and to encourage local medical and specialty societies to cooperate with government efforts in this area.

***PRACTICE MANAGEMENT PROBLEMS?***

**DO ANY OF THESE SOUND FAMILIAR?**

- Declining Patient Volume and Practice Income
- Increasing Overhead
- More Competition Than Ever Before
- Demanding Patients
- Confusion Over Governmental Reimbursement Plans
- Skyrocketing Malpractice Insurance Premiums
- Confusing Contracts from Prepaid Health Plans

While it may not be possible to eliminate all of these problems, it is possible for medical practices to control at least a portion of these challenges through effective Practice Management.

The Professional Practice Division of Toback & Company can provide marketing advice which will increase patient volume; financial tools to increase income and control overhead; reduce office conflict and personnel management problems, reducing employee turnover; and increase physician satisfaction with the practice. Richard E. Kirkpatrick, M.H.S.A., Manager of our Professional Practice Division and a nationally recognized authority on medical practice management can provide you with additional information on the benefits of our services in a no-fee interview. Please call 264-9011 to schedule an appointment.

Richard E. Kirkpatrick

**TOBACK & COMPANY, P.C.**
Professional Practice Division
3200 North Central Avenue, Suite 700
Phoenix, Arizona 85012
(602) 264-9011

**MEDICAL BOOKSTORE**

**MEDICAL BOOKSTORE**
College of Medicine
Arizona Health Sciences Center
Tucson, Arizona 85724
Phone: 626-6669

# A WORD TO THE WHYS

## WHY AMA?

The AMA has tackled the issue of cost effective quality medical care by supporting the development of health care coalitions. The Association believes the best mechanism for keeping health costs down without sacrificing quality or accessibility is through voluntary coalitions in which physicians actively participate. Working to promote high quality, affordable medical care in the United States: it's one more good reason why you should be a part of the AMA.

## WHY AMA?

The AMA has actively sought to attract women as members and leaders in organized medicine. Ongoing AMA projects and concentrated efforts by county, state, and specialty societies have significantly increased the leadership role and membership of women in organized medicine. Strengthening the voice of women in medicine through encouraging active participation: it's one more good reason why you should be a part of the AMA.

## WHY AMA?

Through the AMA library you can have immediate access to a vast store of medical, scientific, and socio-economic information. The library maintains a large collection of books, journals, and microfilm and provides instant on-line access to countless information sources through computerized data bases. The AMA library: it's one more good reason why you should be part of the AMA.

**To Join,** Contact your county or state medical society or write: Division of Membership, AMA, 535 North Dearborn Street, Chicago, Illinois 60610 or call collect, (312) 751-6196.

AMA
AMERICAN MEDICAL ASSOCIATION

AN OUTSTANDING LOCATION □ A REMARKABLE VALUE

# *Bank Sale Presents A Unique Opportunity.*

Practice at a premium location on the shore of Dobson Ranch Lake, part of the Dobson Ranch planned community. Located just south of the Dobson Road and Baseline intersection, a short drive from Desert Samaritan and five other East Valley Hospitals.

Enjoy the tax benefits of an owner-occupied medical office that features easy freeway access, open space, individually signed identity, ample parking at your door and street level entry with in-and-out ease for handicapped patients. Choose from eighteen separate units in seven building clusters.

## Dobson Ranch Professional Center

2058 South Dobson Road □ Mesa, Arizona

Managed and Marketed by
**Lowe Associates, Inc.**

Contact your local Broker or Telephone Peter Koenig, 279-0120

# New Active Members . . .

*The Arizona Medical Association welcomes the following new members:*

COCHISE

**David P. Klein, M.D.**
Diagnostic Radiology
300 El Camino Real, Sierra Vista
University of Illinois
College of Medicine - 1981

MARICOPA

**Robert L. Berman, M.D.**
Anesthesiology
3030 South Rural Road, Tempe
University of Wisconsin
Medical School-Madison - 1966

**Andre C. Matthews, M.D.**
Orthopedic Surgery
6553 East Baywood Avenue
Suite 207, Mesa
University of Cincinnati
College of Medicine - 1980

**George W. Ryback, M.D.**
Anesthesiology
525 West Brown Road, Mesa
Medical College of Wisconsin
Milwaukee - 1977

**Howard B. Somers, M.D.**
Urological Surgery
P.O. Box 1667, Mesa
Fac Med Univ Autonoma
De Guadalajara - 1973

PIMA

**Michael J. Bart, M.D.**
Anesthesiology
3390 North Campbell Avenue
Suite 110, Tucson
University of Texas School
of Medicine-Galveston - 1982

**Ram Gopalan, M.D.**
Psychiatry
1121 West Wetmore Road, Tucson
Topiwala National Medical
College - 1976

**Robert J. Kahler, M.D.**
Obstetrics & Gynecology
P.O. Box 12650, Tucson
Bowman Gray School of Medicine
Wake Forest University - 1980

**Robert G. Salazar, M.D.**
Anesthesiology
5700 East Pima Street
Suite E, Tucson
University of Southern California
School of Medicine - 1979

YAVAPAI

**Gregory Oldani, M.D.**
Urological Surgery
1003 Division Street, Prescott
Ohio State University
College of Medicine - 1975

NEW RESIDENT MEMBERS

MARICOPA

**Ling-Cheng S. Kuo, M.D.**
Psychiatry
Maricopa Medical Center
American University of
The Caribbean - 1981

**Kofi Sepa-Boakye, M.D.**
Obstetrics & Gynecology
St. Joseph's Hospital and
Medical Center
University of California, Los
Angeles School of Medicine - 1984

PHOENIX MANAGEMENT SERVICES INC.

PMS

SINCE 1980

THE Collectors

FOR

MEDICAL • RETAIL • COMMERCIAL

LICENSED • BONDED
FAST • COURTEOUS • PROFESSIONAL
NATIONAL & INTERNATIONAL COLLECTIONS

CALL THE PROFESSIONALS
3530 E. INDIAN SCHOOL RD.

956-3459

# ArMA Financial Services, Inc.

**Products and Services By Your Broker/Dealer**

As a wholly-owned subsidiary of The Arizona Medical Association, it is the sole purpose of ArMA Financial Services to serve our member physicians. We offer investment services by professionals in their field whose goal is to provide you with the quality products and services you would like to attain for yourself ... if you only had the time!

ArMA
FINANCIAL
SERVICES
INC.

## AREAS OF EXPERTISE:

### Pension and Profit Sharing Services

- Design and Restructuring of New and Existing Retirement Plans.
- Annual Administration and Actuarial Services.
- Plan Terminations and IRA Rollovers.
- Plan Documents with Free Legislative Amendment Updates.

### Financial Investment Services

- Registered Investment Advisor Management
- Portfolio Analysis
- Mutual Funds
- Individual Stocks & Bonds

### Significant Savings On

- Brokerage Commissions
- Money Management
- Trustee and/or Custodial Fees

The Arizona Medical Association now sponsors a Section 501 (c) (9) VEBA Trust. This Multiple Employer Trust permits **TAX DEDUCTIBLE** contributions from earned income to an individual plan under ArMA's Master Trust.

Contributions can be in addition to your pension plan, and may be comparable to or even exceed defined benefit pension plan deductions. Earnings in your VEBA Plan Trust are fully **guaranteed** and are **tax deferred**. This exciting qualified employee benefit plan may be right for your practice.

Call ArMA toll-free today ... 1-800-482-3480 outside Phoenix, or 246-8901, Phoenix and ask for: Jere K. LeDesky or Merrill J. Sauriol.

# MAGAZINE SUBSCRIPTIONS AT HUGE SAVINGS

# ARIZONA MEDICAL ASSOCIATION MAGAZINE PROGRAM

*a division of Subscription Services, Inc.*

## 29 Glen Cove Avenue • Glen Cove, New York 11542 • 516-676-4300

Our members qualify for low professional subscription rates for magazines for office reception room use. In addition, many members are educators associated with universities or teaching hospitals and may order magazines at special educator rates. If you wish to select any educator rates, be sure to complete the section of the coupon that requests your affiliated institution. Please note that our list contains the prices in both categories. You may renew or extend your present subscription through the program.

| PUBLICATION | (No. of issues per yr.) | REG. SUBSCR. PRICE | YOUR OFFICE PRICE | YOUR EDUC. PRICE |
|---|---|---|---|---|
| American Health | 10 | 14.95 | 12.95 | 11.95 |
| American Heritage | 6 | 24.00 | 18.00 | 18.00 |
| Amer.Photog.[Special: | 8 iss.] | 5.98 | | 5.98 |
| Americana | 6 | 11.95 | 11.95 | 9.95 |
| ArtNews | 12 | 29.95 | 25.95 | 25.95 |
| Atlantic Monthly | 12 | 9.95 | 9.95 | 9.95 |
| Audio | 12 | 19.94 | 9.97 | 9.97 |
| AUTOMOBILE | 12 | 18.00 | 9.00 | 11.95 |
| Baseball Digest | 12 | 14.95 | 9.97 | 9.97 |
| Basketball Digest | 8 | 9.95 | 7.97 | 7.97 |
| *Better Homes&Gdns | 12 | 14.00 | 7.00 | 14.00 |
| *BICYCLING | 10 | 15.97 | 8.00 | 12.97 |
| Black Enterprise | 12 | 15.00 | 15.00 | 11.95 |
| Boating | 12 | 21.94 | 18.97 | 18.97 |
| Bon Appetit | 12 | 15.00 | 15.00 | 15.00 |
| Bowling Digest | 6 | 12.00 | 9.97 | 9.97 |
| BULLETIN HIST/MED | 4 | 24.00 | 22.00 | 22.00 |
| Car & Driver | 12 | 16.98 | 11.99 | 11.99 |
| child (Fashion) | 6 | 12.00 | 10.00 | 10.00 |
| Changing Times | 12 | 15.00 | 9.97 | 9.97 |
| *Connoisseur | 12 | 19.95 | 10.00 | 19.95 |
| Consumers Reports | 12 | 16.00 | 16.00 | 16.00 |
| *Cosmopolitan | 12 | 24.97 | 15.00 | 24.97 |
| Cruise Travel | 6 | 12.00 | 9.97 | 9.97 |
| Cycle | 12 | 13.98 | 6.99 | 6.99 |
| Cycle World | 12 | 13.94 | 6.97 | 6.97 |
| DISCOVER | 12 | 23.95 | 14.95 | 14.95 |
| Oog Fancy | 12 | 17.97 | 17.97 | 12.97 |
| EBONY | 12 | 16.00 | 9.97 | 9.97 |
| The Economist | 52 | 85.00 | 51.00 | 51.00 |
| *ELLE | 12 | 24.00 | 16.00 | |
| EM (Ebony Man) | 12 | 24.00 | 19.95 | 19.95 |
| ESQUIRE | 12 | 17.94 | 9.95 | 9.95 |
| Essence | 12 | 12.00 | 9.96 | 9.00 |
| EUROPEAN TRAVEL & LIFE | 10 | 24.00 | 12.00 | 16.00 |
| Family Circle | 17 | 14.97 | 9.97 | |
| Family Computing | 12 | 19.97 | 9.99 | 9.99 |
| Family Handyman | 10 | 9.95 | 9.95 | 5.95 |
| Field & Stream | 12 | 15.94 | 7.97 | 7.97 |
| Fifty Plus | 12 | 15.00 | 11.97 | 11.97 |
| Financial World | 26 | 41.95 | 24.94 | |
| Flying | 12 | 18.98 | 15.97 | 15.97 |
| Food and Wine | 12 | 20.00 | 10.00 | 15.00 |
| Football Digest | 10 | 12.95 | 12.95 | 7.97 |
| Forbes | 28 | 45.00 | 45.00 | 29.95 |
| Fortune | 26 | 44.50 | 35.30 | 22.75 |
| Games Magazine | 12 | 15.97 | 15.97 | 15.97 |
| Gentlemens Quartly | 12 | 18.00 | 13.50 | |
| Glamour | 12 | 15.00 | 12.00 | |
| Golf Digest | 12 | 19.94 | 11.98 | 11.98 |
| Golf Illustrated | 10 | 15.00 | 7.97 | 7.97 |
| Golf Magazine | 12 | 15.94 | 9.97 | 9.97 |
| *Good Housekeeping | 12 | 15.97 | 9.97 | 15.97 |
| Gourmet | 12 | 18.00 | 13.50 | 15.00 |

| PUBLICATION | (No. of issues per yr.) | REG. SUBSCR. PRICE | YOUR OFFICE PRICE | YOUR EDUC. PRICE |
|---|---|---|---|---|
| *Harpers Bazaar | 12 | 16.97 | 8.97 | 16.97 |
| Harpers Magazine | 12 | 18.00 | 9.97 | 9.97 |
| Health [Special: | 9 issues] | | 8.97 | 8.97 |
| High Fidelity | 12 | 13.95 | 6.98 | 6.98 |
| Hockey Digest | 8 | 9.95 | 7.97 | 7.97 |
| Home Mechanix | 12 | 11.94 | 8.97 | 8.97 |
| The Homeowner[Special: | 6 iss] | | 8.97 | 8.97 |
| Home Viewer | 12 | 18.00 | 11.97 | 11.97 |
| Hot Rod | 12 | 13.94 | 8.97 | 8.97 |
| House and Garden | 12 | 24.00 | 18.00 | |
| *House Beautiful | 12 | 15.97 | 7.99 | 15.97 |
| Inc. | 12 | 24.00 | 12.00 | 12.00 |
| Inside Sports | 12 | 18.00 | 11.97 | 11.97 |
| Jerusalem Post | 24 | 18.46 | 18.46 | 15.97 |
| Jet | 52 | 36.00 | 26.00 | 26.00 |
| LADIES' HOME Journal | 12 | 19.95 | 11.97 | 9.98 |
| LITERATURE & MED. | 1 | 12.95 | 10.95 | 10.95 |
| LIFE | 12 | 32.50 | 16.25 | |
| M (Civilized Man) | 12 | 24.00 | 19.95 | |
| Mademoiselle | 12 | 15.00 | 12.00 | |
| McCalls | 12 | 11.95 | 7.95 | |
| METROPOLITAN HOME | 12 | 18.00 | 9.00 | 9.00 |
| Modern Photography | 12 | 13.98 | 7.98 | 6.99 |
| Money | 12 | 34.95 | 16.00 | 15.99 |
| Mother Jones | 12 | 24.00 | 16.00 | 16.00 |
| Motor Trend | 12 | 13.94 | 7.97 | 7.97 |
| MS Magazine | 12 | 16.00 | 10.97 | 10.97 |
| Nation's Business | 12 | 22.00 | 12.97 | 12.97 |
| N.E.Journal of Med. | 52 | | 66.00 | |
| New Republic | 48 | 56.00 | 56.00 | 28.00 |
| New Woman | 12 | 15.00 | 9.95 | 11.97 |
| New Yorker | 52 | 32.00 | 32.00 | 20.00 |
| New York | 50 | 33.00 | 16.50 | 19.98 |
| *NEWSWEEK | 52 | 41.00 | 20.80 | 21.80 |
| OMNI | 12 | 24.00 | 15.96 | 15.96 |
| 1001 Home Ideas[Spec'l: | 8 iss] | 11.97 | | 11.97 |
| Organic Gardening | 12 | 12.97 | 11.97 | 11.97 |
| Outdoor Life | 12 | 13.94 | 7.97 | 7.97 |
| Outside | 10 | 16.00 | 12.00 | 8.97 |
| Ovation | 12 | 18.00 | 10.00 | 10.00 |
| PARENTING | 10 | 18.00 | 9.00 | |
| Parents MAGAZINE | 12 | 18.00 | 9.00 | 11.95 |
| Penthouse | 12 | 36.00 | 30.00 | 30.00 |
| People | 52 | 56.00 | 56.00 | 30.95 |
| Personal Computing | 12 | 18.00 | 18.00 | 11.97 |
| Petersens Photgrph | 12 | 13.94 | 6.97 | 6.97 |
| Playboy | 12 | 25.00 | 19.00 | 19.00 |
| *Popular Mechanics | 12 | 13.97 | 7.00 | 13.97 |

| PUBLICATION | (No. of issues per yr.) | REG. SUBSCR. PRICE | YOUR OFFICE PRICE | YOUR EDUC. PRICE |
|---|---|---|---|---|
| Popular Photogrphy | 12 | 11.97 | 6.99 | 6.99 |
| Popular Science | 12 | 13.94 | 7.97 | 7.97 |
| *PRACTICAL HOMEOWNER | 9 | 12.97 | 6.50 | 9.97 |
| *PREVENTION | 12 | 13.97 | 7.00 | 13.97 |
| PSYCHOLOGY TODAY | 12 | 15.99 | 8.00 | 8.00 |
| Reader's Digest | 12 | 15.41 | 15.41 | 15.41 |
| *Redbook | 12 | 11.97 | 6.97 | |
| Road and Track | 12 | 19.94 | 14.99 | 14.99 |
| Robb Report | 12 | 65.00 | 65.00 | |
| *RUNNER'S WORLD | 12 | 19.95 | 10.00 | 12.97 |
| Sail | 12 | 21.75 | 21.75 | 21.75 |
| SAILING WORLD | 12 | 21.75 | 10.88 | 10.88 |
| Saturday Eve. Post | 9 | 12.97 | 12.97 | 12.97 |
| Savvy | 12 | 18.00 | 9.00 | 9.00 |
| Self | 12 | 15.00 | 12.00 | |
| Seventeen | 12 | 13.95 | 13.95 | 13.95 |
| Ski | 8 | 11.94 | 6.97 | 6.97 |
| Skiing | 7 | 9.98 | 5.97 | 5.97 |
| Skin Diver | 12 | 13.94 | 7.97 | 7.97 |
| SPORT | 12 | 12.00 | 7.97 | 7.97 |
| Sporting News | 55 | 55.95 | 29.97 | |
| *Sports Afield | 12 | 13.97 | 6.99 | 13.97 |
| SPORTS ILLUSTRATED | 54 | 58.80 | 34.00 | 29.45 |
| Stereo Review | 12 | 9.98 | 4.99 | 4.99 |
| Sunset | 12 | 14.00 | 11.20 | |
| S.Porters Pers.Fin. | 12 | 19.97 | 11.97 | |
| TAXI (Fashion) | 12 | 24.00 | 17.97 | 17.97 |
| Teen | 12 | 12.95 | 7.95 | 7.95 |
| Tennis | 12 | 17.94 | 8.97 | 8.97 |
| TIME | 52 | 58.25 | 29.25 | 29.12 |
| *Town & Country | 12 | 24.00 | 12.00 | 24.00 |
| Travel & Leisure | 12 | 25.00 | 12.50 | 18.00 |
| TV Guide | 52 | 31.20 | 29.90 | 26.00 |
| UNIQUE HOMES | 6 | 29.97 | 19.97 | 19.97 |
| USA Today | 260 | 130.00 | 91.00 | 86.95 |
| U.S.News & WORLD REPORT | 52 | 34.50 | 17.25 | 17.25 |
| US Magazine | 26 | 23.95 | 12.98 | 12.98 |
| Vegetarian Times | 12 | 19.95 | 14.95 | 14.95 |
| Video | 13 | 12.00 | 8.97 | 8.97 |
| Video Review | 12 | 12.00 | 6.97 | 6.97 |
| Vogue | 12 | 24.00 | 21.00 | |
| W Magazine | 26 | 26.00 | 23.00 | 17.95 |
| Weight Watchers | 12 | 13.97 | 11.97 | 11.97 |
| Woman's Day | 17 | 16.97 | 16.97 | 16.97 |
| Women's Sports | 12 | 12.95 | 7.97 | 8.95 |
| WORKING MOTHER | 12 | 11.95 | 7.95 | |
| Working Woman | 12 | 18.00 | 12.00 | 15.00 |
| World Tennis[Special: | 6 issues] | 5.97 | | 5.97 |
| WORLD TRAVELING | 4 | 11.00 | 9.95 | 9.95 |
| YM | 12 | 14.00 | 7.00 | 10.95 |

* BUSINESS CARD NEEDED FOR OFFICE PRICE

**ArMA MAGAZINE PROGRAM**
**29 Glen Cove Avenue**
**Glen Cove, New York 11542**

NAME _____

ADDRESS _____

CITY _____ STATE _____ ZIP _____

Complete for Educator rates:

_____ _____
Name of Educator Affiliated Hospital / School

☐ VISA
☐ M/C No. _____ Exp. Date _____

You may pay by check or credit card. Please make checks payable to ArMA Magazine Program.

| NAME OF PUBLICATION | YEARS | PRICE |
|---|---|---|
| | | |
| | | |
| | | |
| | | |
| | | |
| | TOTAL | |

**Terms:** Subscriptions are one year unless otherwise noted
Prices subject to publishers' changes
**Guarantee:** Our prices are the lowest, our service the best.
**Renewals:** Please send the address label from your magazine at least 8 weeks in advance of expiration date.
**New Orders:** Publishers take from 8 to 12 weeks to start your subscription.

AZMD287

# Classified Advertising


**We Bind Your**
**PERIODICALS**

Preserve your medical journals as beautifully bound books. Choose from 30 different colors of durable Library Buckram.

**$14.50 per volume, (name imprint $1.00)**
**$15.50 Imitation Leather, (rules .50 each)**

Inquire about quantity discounts. **Free** local pickup and delivery on 10 volumes or more. Minimum order is $25.00.

**ROSWELL BOOKBINDING**
**2614 North 29th Avenue**
**Phoenix, Arizona 85009 ■ (602) 272-9338**

P A S

*"People, The Reason And The Key"*

**Personnel Administration Services, Inc.**
3080 North Civic Center, Suites 11 & 12
Scottsdale, Arizona 85251

(602) 947-8053
(602) 947-8375

**EDWARD N. PHILLIPS**
President

**ASSOCIATED LABORATORY CONSULTANTS, INC.**
SPECIALIZING IN QUALITY ASSURANCE

LABORATORY
- DEVELOPMENT
- IMPLEMENTATION
- MANAGEMENT

PERSONNEL
- RECRUITMENT
- EVALUATION
- EDUCATION

P.O. BOX 502 • SCOTTSDALE, AZ 85252 • (602) 990-0068

**DANNY T. SEIVERT**
**INSURANCE, INC.**
Professional Programs
for Professional People
**70 E. Mitchell Dr., Suite 6**
**Phoenix, Arizona 85012**
**263-9090**

**IMMEDIATE CASH**
We Will Fund Your
Medical Insurance Receivables
**NOW**
Our Service Will Solve Your
CASH-FLOW Concerns
Call Kevin at "the MONEY COMPANY"
(602) 968-3747

YOU WORKED HARD

FOR THAT DIPLOMA..
why not have it laminated?

It will last a lifetime....
**THE PLAQUE SHOP**

Wood plaques — Ready to hang
No glass to break — Moisture proof
Dirt proof — Impressive.
Our plaques are manufactured locally.

**ARIZONA LAMINATING SERVICE, INC.**
**7231 East First Avenue**
**Scottsdale, Arizona 85251**
**(602) 945-9338**

**MEDICAL SPACE AVAILABLE**
**at the**
**PROFESSIONAL CENTER**
2610 West Bethany Home Road (At I-17)

Managed by
Public Management & Appraisal
(602) 249-9072

## PROFESSIONAL OPPORTUNITIES

### CLAYPOOL

Gila Medical Services Corporation seeks a **Family Practice** physician to provide medical care including **OB** and **Deliveries**. Gila Medical Services operates a multi-specialty group practice which provides routine primary medical care to the service area population of 29,000, with x-ray and lab services available on site. Salary and benefits commensurate with experience, with paid relocation expense. Claypool, Arizona is located almost equidistant from Phoenix and Tucson in Gila County. Reply: Peggy A. Broussard, AHPR, 3131 E. Second Street, Tucson, Arizona 85716 (602) 626-7946.

### CASA GRANDE

Expanding multi-specialty clinic is seeking **BE/BC Family Practitioner** willing to do OB. Salary plus bonus with opportunity to buy-in to the partnership within 12 months. Paid malpractice and paid vacation. Clinic equipped with full service Radiology Department, Laboratory, Nursing Staff, 22 exam rooms and private offices for doctors. New 100-bed hospital within 2 miles. Casa Grande is a rapidly growing community of 20,000 with a trade area of 40,000 located halfway between Phoenix and Tucson. The advantage of living in a small town, convenient to major metropolitan areas without the pollution and congestion problems. Send your CV to: Peggy A. Broussard, AHPR, 3131 E. Second Street, Tucson, Arizona 85716 (602) 626-7946.

### SPECIAL OPPORTUNITY

For energetic, bright, open-minded physician. Grow rapidly with little expense and high percentage. Established practices need qualified family M.D. Able to work in multi-disciplined offices Tempe — Scottsdale. Call Dr. Bruce Lubitz at Community Holistic Health Clinic. (602) 968-7767.

### RADIOLOGIST

Board Certified, seeking to relocate, University trained, extensive experience all phases of radiology including administration and teaching. Arizona license — interested Tucson area. Write Arizona Medical Association, P.O. Box 40687, Phoenix, Arizona 85013.

### FAMILY PRACTICE

To do family care in multi-specialty clinic and satellite clinic. Full in-house lab and x-ray. Delightful community, good schools and recreation. Reply to: P.O. Box 0955, C/O Arizona Medicine, 810 West Bethany Home Road, Phoenix, Arizona 85013.

## MEDICAL OFFICES

### OFFICES FOR LEASE

1840 E. Baseline, Tempe, Arizona (East of McClintock) close to Hospitals, 1/2 mile from Superstition Freeway, lush landscaping, competitive rates with free rent, excellent parking and access. Contact Michael Beall, **L.J. Hooker International** (602) 956-5250.

### OFFICE SPACE

**Scottsdale office for lease:** Excellent, **New** 2000 ft., prof. designed, includes two Private Offices, Recpt. Rm., Admn./Accounting, two Prep Rms., 4 Exam Rms., Lab and two toilets. 7330 East Earll Dr., just off Civic Plaza. Call Art Kappelmann, **The Westwind Company** — (602) 945-4071.

### MEDICAL OFFICE TO RENT

1500 Sq. feet Modern office space in Paradise Valley, AZ (Phoenix), available July 1, 1987. Ideal for Family Practice, Specialists, near 2 major hospitals. Reply: 3326 E. Sweetwater, Phoenix, Arizona 85032.

## REAL ESTATE

### MAYO DOCTORS

Must see this exceptional 3-bedroom, 2½ bath, better-than-new custom home featuring two fireplaces, cathedral and vaulted ceilings, plant shelves and much more. Expansive master suite, split for privacy, custom designed security fenced pool. Cool neutral decor always immaculately maintained inside and out. Full tile roof and two-car garage. Offered at $238,000. Call Linda O'Kelley at **John Hall & Associates.** (602) 948-0550.

### FAMILY/EXECUTIVE HOME

Dramatic 4-bedroom, 2-bath, 2344 sq
on 1/4 acre in Scottsdale, Arizona. Bl
construction, see-thru fireplace in liv
room with conversation pit, vaulted c
ings, monitored security system, gar
doors, kitchen bay window, irriga
landscape, decorative indoor and c
door lighting, many other upgrac
Energy efficient, near new. 56th St
Bell. Asking $165,900, favorable fina
ing by owner. (602) 992-6780.

## MISCELLANEOUS

### MAXIMIZE YOUR PRACTICE POTENTIAL

Enrich the quality and prosperity of y
personal and professional life. Your p
fession is constantly changing. Let
help you stay on the cutting edg
trends and technology and keep y
practice growing. **You Can Choose S
cess.** Contact Alanna Johnson at (6
956-9638 for practice developm
consultation.

### FOR SALE

Well-maintained Del Mar Avio
Model 655 Holter Scanner and 3 M
445 recorders as well as battery char
$60,000. Contact Mary Boehm (0
848-5800

### LARGE LOANS

Since 1966 specializing in large loa
physicians nationwide from $15,00
to $90,000.00. Long repayment ter
fixed interest rates. Commitments
ally within 48 hours. Woodside Ca
Corp., Woodside Capital Building,
Box 368, Woodland Hills, CA 9136
further information call (800) 423-5

### PHYSICIANS SIGNATURE LOA

Loans to $50,000. Competitive
rates. No collateral. Up to seven yea
repay with no pre-payment pena
Prompt, courteous service. Physi
Service Association, Atlanta, Ge
(800) 241-6905. Serving MDs for ov
years.


**Valley Researchers & Library Services**

**1946 E. El Moro Street**
**Mesa, Arizona 85204**
**(602) 892-2443**

**MEDLINE searches, journal-articles, document-delivery, library organization, Grateful Med and MEDLARS training.**

# Clorazepate Use May Prevent Alcohol Withdrawal Convulsions

VICTOR G. HADDOX, MD, JD; T. GEORGE BIDDER, MD; LESTER E. WALDRON, *and* PATRICIA DERBY, *Sepulveda, and* SUSAN M. W. ACHEN, MPH, RN, *Van Nuys, California*

*Clorazepate dipotassium was administered orally for the five-day prophylactic treatment of potential, incipient and overt withdrawal signs and symptoms in 226 patients on admission to an inpatient alcohol treatment unit. Conservative estimates based on these patients' histories and on literature reports predicted that between 7 and 40 (3% to 18%) of these persons would be expected to have a withdrawal convulsion. No patients experienced convulsions. This complete absence of seizures suggests that clorazepate is effective in counteracting convulsive and other manifestations of the alcohol withdrawal syndrome.*

(Haddox VG, Bidder TG, Waldron LE, et al: Clorazepate use may prevent alcohol withdrawal convulsions. West J Med 1987 Jun; 146:695-696)

The use of alcoholic beverages to the extent that physical dependence develops and withdrawal phenomena occur is a problem encountered in a relatively small percentage of persons who drink. Because of the extensive use of alcoholic beverages throughout the world, however, physicians frequently need to treat patients who are physically dependent on alcohol and who manifest withdrawal signs and symptoms or who have the potential for having these problems.

Physical dependence on alcohol is a major problem in those who seek help with alcohol misuse by enrolling in an alcohol treatment program. In the Sepulveda Veterans Administration Medical Center (VAMC) Alcohol Treatment Unit, a 35-day inpatient program, about two thirds of the 400 patients admitted annually to this facility show signs and symptoms of an alcohol withdrawal syndrome to the extent that medication to alleviate the symptoms is indicated.

In view of the prevalence of physical dependence on alcohol, it is essential to develop effective prophylactic methods for treating this problem that are safe and do not interfere with the physical, emotional and social rehabilitation that constitutes the major goals of alcohol treatment programs.

In this article we report a retrospective study of the use of the benzodiazepine, clorazepate, in 226 patients newly admitted to an inpatient alcoholism treatment unit who were either acutely intoxicated or experiencing an alcohol withdrawal syndrome. Clorazepate dipotassium was used prophylactically to treat potential, incipient and overt withdrawal symptoms. The anticonvulsant action of this agent, its long duration of action, its mild sedative effect, its high margin of safety and its cross-tolerance with alcohol have provided safe and effective therapy for patients who are frequently debilitated and who invariably have alcohol-related medical disorders.

The fact that no convulsive episode occurred in the 226 patients whose potential withdrawal syndrome was treated prophylactically with clorazepate is of clinical significance in view of a history of withdrawal convulsions in 18% of this group and literature estimates that grand mal convulsions occur in from 3% to 18% of alcoholic patients during withdrawal when no prophylaxis is given.

## Methods

The Sepulveda VAMC Alcohol Treatment Unit is a 30-bed facility that provides an initial five-day detoxification period followed by a comprehensive 30-day program having the objectives of medical and psychological evaluation and treatment, rehabilitation, life-structuring and providing alternatives to drinking. During the 18-month period of the present retrospective study, 226 patients were detoxified with clorazepate. Of these patients, 41 (18%) had a well-documented history of at least one grand mal convulsion related to withdrawal from alcohol. A history of delirium tremens was present in 62 of these patients (27%), and virtually all had experienced withdrawal tremulousness in the past.

Each patient was detoxified with a regimen that included

- Magnesium sulfate, 2 grams given intramuscularly immediately upon admission, followed by 1 gram given intramuscularly every four hours for three doses;
- Clorazepate dipotassium, 15 mg given orally four times a day (day 1), three times a day (day 2), twice a day (day 3) and at bedtime (day 4); 7.5 mg at bedtime (day 5). In patients showing withdrawal signs and symptoms with this dose schedule, supplemental "as needed" oral doses of clorazepate, 15 mg every four to six hours, were available during the first three hospital days. About 25% of the patients required at least one supplemental dose.

This detoxification phase was followed by a 30-day rehabilitative period.

From the Alcohol Treatment Unit (Dr Haddox and Mr Waldron), the Department of Psychopharmacology (Dr Bidder), the Department of General Medicine (Mr Waldron) and the Research Service (Ms Derby), Veterans Administration Medical Center, Sepulveda; the Department of Psychiatry (Drs Haddox and Bidder), University of California, Los Angeles, School of Medicine, and the Valley Presbyterian Hospital Olmstead Memorial (Ms Achen), Van Nuys, California.

Reprint requests to Victor G. Haddox, MD, JD, Alcohol Treatment Unit, Veterans Administration Medical Center, 16111 Plummer St, Sepulveda, CA 91343.

ABBREVIATIONS USED IN TEXT

CNS = central nervous system
VAMC = Veterans Administration Medical Center

## Results and Discussion

There was no occurrence of a grand mal convulsion in the 226 patients receiving the prophylactic clorazepate detoxification regimen.

The absence of seizure complications in this population of patients in the period immediately following the cessation of drinking is noteworthy for several reasons. First, these patients had a history of drinking heavily for several months before admission; 67% had clinically significant concentrations of alcohol—that is, more than 0.1 grams per dl—at the time of admission. Second is the expectation that seizures are likely to occur in from 3% to 18% of patients with severe alcoholism who stop drinking.[1,2] Third is the past history in 41 study patients (18%) of one or more recorded convulsive episodes during withdrawal from alcohol. The significance of this type of past history in predicting the likelihood of a convulsion occurring during withdrawal from alcohol is emphasized by the work of Tartara's group.[3] In a retrospective study these workers reported an incidence of convulsive manifestations in 10% of alcoholic patients during withdrawal. When they excluded cases with preexisting, potentially epileptogenic lesions, this percentage fell to 7%.

On the basis of these data, it can be anticipated that between 7 (3%) and 40 (18%) of the 226 study patients would have progressed to stage 3 in the alcohol withdrawal syndrome (see Table 1) and would have manifested withdrawal seizure activity if no prophylactic treatment had been instituted. It is of considerable significance that the symptoms in stage 2 among those patients were reduced, and more important, that no patient progressed to stage 3.

TABLE 1.—*Alcohol Withdrawal Syndrome**

| *Time of Appearance After Stopping or Significantly Reducing Alcohol Intake* | *Symptoms* |
|---|---|
| Stage 1 | |
| 6 to 8 hours | Tremulousness, anxiety, startle reaction, autonomic hyperactivity (heart rate, blood pressure, diaphoresis, nausea, vomiting), hyperreflexia, craving for alcohol and other CNS depressants, sleep disturbance. Wernicke's encephalopathy and Korsakoff's disease present, but usually masked by more dramatic and acute symptoms |
| Stage 2 | |
| 24 hours | Hallucinations complicating persisting stage 1 phenomena, usually auditory or visual. May be other types and especially common at night when eyes are closed; need to differentiate from hallucinosis—an alcohol-related toxic psychosis |
| Stage 3 | |
| 7 to 48 hours | Grand mal convulsions that complicate persisting phenomena: generally multiple—2 to 6 in a 6- to 8-hour period, brief postictal period, probability of delirium tremens |
| Stage 4 | |
| 7 hours to 14 days | Global confusion complicating autonomic hyperactivity and hallucinations (delirium tremens), profound hyperthermia, hypertension, fluid electrolyte imbalance, vascular collapse, death |

CNS=central nervous system

*Adapted and modified from Sellers and Kalant[4] and several other sources.

The development of tolerance and physical dependence to central nervous system (CNS) depressants such as alcohol is considered to be an adaptive or compensatory reaction that counters the depression of neuronal functions produced by these agents.[4] Discontinuance of, or an abrupt decrease in, alcohol ingestions leaves these stimulatory compensatory reactions unopposed, with a resulting increase in the neuronal excitability responsible for most of the signs and symptoms of the alcohol withdrawal syndrome. The grand mal convulsions that occur in the alcohol withdrawal syndrome are a striking manifestation of this hyperexcitability.

The well-established effects of the benzodiazepines in ameliorating signs and symptoms of the alcohol withdrawal syndrome involve several known pharmacologic actions of these compounds. These include the capacity for replacing the CNS depressant, alcohol, to which tolerance and physical dependence have been acquired. Of special relevance to the present study is these agents' anticonvulsant action[5] that is exerted on the propagation of the seizure process, rather than on the seizure focus, and that is considered to involve presynaptic $\gamma$-aminobutyrate-minergic mechanisms.[6]

Clorazepate has several pharmacologic attributes that make it a very useful agent for oral prophylactic treatment of the alcohol withdrawal syndrome. It has a long duration of action as a result of its in vivo conversion to desmethyldiazepam.[7] This avoids the risk that a withdrawal syndrome, such as frequently occurs with single doses of benzodiazepines that have a short half-life,[8] will intensify the alcohol withdrawal syndrome. The high margin of safety of clorazepate is reassuring when treating persons who have a high incidence of medical disorders. Finally, clorazepate lacks the euphorigenic, addiction-promoting action of certain benzodiazepines such as diazepam, chlordiazepoxide and alprazolam. This advantage, which is attested to by the unusual fact that no patient receiving clorazepate asked to have the drug therapy continued after the detoxification period was completed, is very important for its use in a group that has a predilection for drug dependency.

The occurrence of convulsions during alcohol withdrawal indicates a substantial degree of physical dependence and portends the possibility that delirium tremens can occur. Thus, clorazepate provides effective oral prophylactic therapy for this serious, unpredictable and potentially fatal complication of alcohol withdrawal. The safety and convenience of clorazepate make feasible its use in all patients requiring detoxification.

### REFERENCES

1. Shaw GK: A guide to drug treatment of alcoholism, *In* Sandler M (Ed): Psychopharmacology of Alcohol. New York, Raven Press, 1980, pp 202-203

2. Chan AKW: Alcoholism and epilepsy. Epilepsia 1985; 26:323-333

3. Tartara A, Manni R, Mazella G: Epileptic seizures and alcoholism—Clinical and pathogenic aspects. Acta Neurol Belg 1983; 83:88-94

4. Sellers DM, Kalant H: Pharmacotherapy of acute and chronic alcoholism and alcohol withdrawal syndrome, chap 42, *In* Clark WG, DelGuidice J (Eds): Principles of Psychopharmacology, 2nd Ed. New York, Academic Press, 1978, pp 726-740

5. Browne TR, Penry JK: Benzodiazepines in the treatment of epilepsy. Epilepsia 1973; 14:277-310

6. Haefely WE: Central action of benzodiazepines. Br J Psychiatry 1978; 133:231-238

7. Greenblatt DJ, Shader RI, Harmatz JS, et al: Self-rated sedation and plasma concentrations of desmethyldiazepam following single doses of clorazepate. Psychopharmacology (Berlin) 1979; 66:289-290

8. British Medical Association, Committee on the Review of Medicines—Systematic review of the benzodiazepines. Br Med J [Clin Res] 1980; 280:910-912

# Increased Use of Medical Services and Antibiotics by Children Who Claim a Prior Penicillin Sensitivity

MICHAEL J. KRAEMER, MD; HOPE CAPRYE-BOOS, MS, ARNP, *and* HENRY S. BERMAN, MD, *Spokane, Washington*

*On surveying 3,467 children (ages 0 to 19 years) who were members of a health maintenance organization in Spokane, Washington, we found that 95 of 1,497 respondents (6.3%) claimed a past intolerance to penicillin-like agents. We investigated the costs of providing medical care for these 95 children and a random sample of 187 children who did not claim prior penicillin sensitivity. During a two-year period of observation, the children who claimed prior penicillin reactions had a significant increase in the average number of medical visits, the average number of antibiotic prescriptions, the average wholesale cost of antibiotic prescriptions and the average antibiotic cost per patient per month of observation. These children have an increased exposure to antibiotics that may increase their risk for adverse drug reactions.*

(Kraemer MJ, Caprye-Boos H, Berman HS: Increased use of medical services and antibiotics by children who claim a prior penicillin sensitivity. West J Med 1987 Jun; 146:697-700)

Penicillin hypersensitivity reactions are common. They usually appear as a drug-induced exanthem but can occasionally be an explosive, life-threatening systemic reaction. Penicillins remain the most common cause of drug-induced anaphylaxis,[1,2] resulting in several hundred drug-related deaths each year.[3]

Penicillin hypersensitivity from oral or parenteral exposures to these drugs may develop in children as well as in adults. The actual prevalence in the pediatric age group is unclear although estimates range from 5% to 20%. Only a minority of the patients who claim a penicillin hypersensitivity actually have a true allergic sensitivity. In a recent clinical skin-testing trial, only 8.75% of children who claimed some prior reaction had positive skin tests (which implies a current allergic potential), and in only an additional 1% of those who did not react to skin tests did an exanthem develop with a ten-day course of penicillin.[4] In many children a transient rash or gastrointestinal reaction can appear either from the infection itself or from a toxic reaction to the antibiotic. If improperly interpreted as an allergic reaction, the child would be labeled as "penicillin-allergic." He or she would then be encouraged to use alternative antibiotics like sulfonamides, erythromycins, tetracyclines or cephalosporins.

This research was undertaken to study the subset of children who claim a prior sensitivity to penicillin without regard to the validity of their claims. We wished to define any discriminating characteristics for the children who claim this sensitivity and to assess the impact of this claim on the cost of their medical care.

## Patients and Methods

### *Allergy Questionnaire*

We designed a questionnaire to assess the prevalence of common childhood allergic disorders: chronic dermatitis, allergic rhinitis, asthma, food hypersensitivities, stinging insect reactions and penicillin sensitivity. This was mailed to the parents of 3,467 children (ages 0 to 19 years), approximately 50% of the membership of a health maintenance organization, Group Health of Spokane (Washington). The questionnaire included a form containing the necessary elements of informed consent as approved by Group Health of Spokane that was signed by the parent or guardian of the child.

Of the 3,467 children sampled, 1,497 completed questionnaires were returned (43.2%). Parents who answered "yes" to "Has your child ever had a reaction to penicillin-like antibiotics?" were placed in the "claims penicillin sensitivity" category (N = 95). For comparisons, we selected a random sample of 187 children whose parents answered "no" to this question.

### *Medical Records Review*

We reviewed the medical records for the two years preceding the time of the survey, noting any documentation of drug allergy claims in the drug allergy decal on the front of the chart, the patient data base and the ongoing progress notes. We recorded the total number of medical visits and antibiotic prescriptions during this two-year interval. The cost of each antibiotic prescription was determined by multiplying the prescription size by the wholesale drug cost

From the Spokane Allergy and Asthma Clinic (Dr Kraemer), the Intercollegiate Center for Nursing Education (Ms Caprye-Boos) and the Group Health of Spokane, Spokane, Washington (Dr Berman).

Reprints are not available.

during that year. The average monthly antibiotic cost for each child was determined by dividing the total drug costs by the total number of months of membership during that two-year observation period. For children who joined the health plan during the two-year interval and for children who reacted to penicillins during this interval, we used information only from the remaining months in the two-year interval of observation.

*Statistical Analysis*

Age and sex, claims of other allergic conditions, number of medical visits, number of antibiotic prescriptions obtained and the cost of antibiotics were compared for patients and controls. The mean and range of these variables are listed in the results. The absolute number and percentage are listed for proportions. For statistical analyses we used the Student's *t* test for age, the Wilcoxon signed ranks test for variables that were not normally distributed and the $\chi^2$ test for proportions. A two-tailed probability was assumed when determining significance levels.

## Results

A total of 1,497 persons returned the survey (43.2%). Of these, 95 children claimed a prior penicillin hypersensitivity (6.3%). Penicillin was the drug most often implicated for causing this reaction, although reactions were also claimed for ampicillin, amoxicillin and bacampicillin hydrochloride. In most instances (87%) the reaction occurred after oral ingestion of the drug. With the design of our study, we could not determine if the rate of sensitization was greater with the oral or the parenteral route. Most of the reactions occurred in younger children (from birth to 3 years of age). The median time from the onset of treatment to the appearance of the reaction was one day, the range was up to nine days. The most common reactions were a pruritic red rash (53%), a nonpruritic fine papular red rash (38%) and large blotchy hives or angioedema (14%). Only four children recounted symptoms consistent with anaphylaxis. The median interval from the time of the reaction to the time of the survey was four years (range 0.1 to 18.6 years). The median age at the time of the reactions was 2.2 years (range 0.2 to 16.5 years). In this survey, 28 children who had their adverse penicillin reaction during the two-year observation period (incident cases) at the time of reaction ranged in age from 0.9 to 16.2 years (median age 1.8 years). None of these patients were admitted to hospital during this two-year interval. A physician confirmed that the rash was allergic in nature in 62 of the children. In none of the 95 cases was more than one suspected penicillin reaction reported. None had specific allergy skin testing to confirm their suspected penicillin hypersensitivity.

Of the 95 who claimed prior reactions on our survey, only 59% (56) had any documentation of their claim in the medical record. This could include a drug-allergy-alert sticker on the front of the chart (47% [45]), an adverse drug reaction claim in the patient data-base section of the med-

TABLE 1.—*Clinical Characteristics of Patients and Controls*

| *Clinical Characteristics* | *Patients, N=95* | *Controls, N=186* | P *Value* |
|---|---|---|---|
| Age | | | |
| Mean, years | 8.93 | 8.91 | NS |
| Range, years | 0.8 to 19.5 | 0.4 to 19.5 | ... |
| Sex | | | |
| Male, No. (%) | 51 (54) | 90 (49) | NS |
| Female, No. (%) | 44 (46) | 96 (51) | ... |
| Allergic diagnoses | | | |
| Chronic pruritic dermatitis, No. (%) | 17 (18) | 17 ( 9) | <.05 |
| Allergic rhinitis, No. (%) | 20 (21) | 18 (10) | <.01 |
| Asthma, No. (%) | 17 (18) | 8 ( 4) | <.001 |
| Food hypersensitivity, No. (%) | 11 (12) | 12 ( 6) | NS |
| Insect sting allergy, No. (%) | 4 ( 4) | 9 ( 5) | NS |
| Total physician visits in the 24-month observation period | | | |
| Mean, No. visits | 5.49 | 3.27 | <.001 |
| Range, No. visits | 0 to 39 | 0 to 19 | ... |
| Months of observation during the 24-month period | | | |
| 0.0 to 5.9, No. (%) | 11 (12) | 17 ( 9) | |
| 6.0 to 11.9, No. (%) | 15 (16) | 34 (18) | |
| 12.0 to 17.9, No. (%) | 14 (15) | 19 (10) | |
| 18.0 to 24.0, No. (%) | 55 (58) | 116 (62) | |
| Total antibiotic prescriptions in the 24-month period | | | |
| Mean | 1.73 | 0.80 | <.001 |
| Range | 0 to 14 | 0 to 9 | |
| Average antibiotic prescription costs per patient during 24-month period | | | |
| Mean, $ | 4.60 | 1.75 | <.001 |
| Range, $ | 0.00 to 59.92 | 0.00 to 21.99 | ... |
| Average antibiotic prescription costs per patient per month of observation | | | |
| Mean, $ | 0.36 | 0.12 | <.001 |
| Range, $ | 0.00 to 7.27 | 0.00 to 4.31 | ... |

NS=no significance

ical record (26% [25]) or a specific notation of a drug allergic reaction in the patient progress notes (22% [21]).

Of the 187 control patients, only one patient who had no prior history of drug hypersensitivity on our survey had claimed an intolerance to penicillin-like agents on the patient data-base section of the chart (making a survey false-negative rate of 0.5%). This patient was excluded from the analysis.

Both patients and controls had similar ages (see Table 1). There was no significant sex difference. A history of chronic dermatitis, allergic rhinitis and asthma was significantly more common in the patient group. A history of food hypersensitivity and of stinging insect reactions was not different. There was a significant difference in the average number of medical visits during the two-year period of observation: 5.49 for patients and 3.27 for controls (Table 1). There was no difference in the number of months of observation between the two groups. A significant difference occurred in the average number of antibiotic prescriptions: 1.73 versus 0.80. There was also a significant difference in the average total cost per person of antibiotic prescriptions issued during the two years—$4.60 versus $1.75—and in the average antibiotic costs per month of observation—$0.36 versus $0.12. The range of these cost categories was broad, so nonparametric tests were used to determine the significance of the differences. In both groups, the number of antibiotic prescriptions written was maximal in the children younger than 4 years (135 prescriptions for 69 children).

During the two-year period of observation, 104 courses of non-penicillin antibiotics were issued to the children who claimed a past penicillin sensitivity, and 31 courses of penicillins were given to the same group. None of these patients who received the penicillin had documentation of any alleged penicillin sensitivity in their chart. Only one of these antibiotic courses resulted in a rash and subsequent withdrawal of the drug. There were no other adverse outcomes or allergic-like sensitivities noted with any of the penicillin-alternative antibiotics administered to these children.

## Discussion

Several risk factors have been associated with the claim of a prior penicillin reaction. Young children and middle-aged adults are at an increased risk of a penicillin allergy developing.[5] The median age of initial penicillin reaction for our group was younger than 2 years. It is likely that the increased incidence of penicillin reactions in this younger group is at least partly explained by this age group's increased exposure to antibiotics. The association of claiming a penicillin reaction with other allergic disease is controversial. Asthma and hay fever have not been more common in persons who actually react on skin tests to penicillins.[6,7] Nonetheless, many earlier series have suggested a higher rate of claiming penicillin allergy in persons with other allergic disorders.[8,9] It would seem that the likelihood of persons to claim a prior drug sensitivity is directly related to the likelihood of their being exposed and thus to being sensitized to that drug. It is possible that allergic patients are more likely to claim this sensitivity because of an increased exposure to penicillins to treat infectious dermatitis, purulent otitis and sinusitis. An alternative explanation is that this subgroup of allergic patients represents persons in whom cutaneous or gastrointestinal symptoms develop more easily due to any number of nonallergic exposures, like infections, fevers or toxic reactions to drugs. We could not discern if a "diagnostic bias" also led parents of allergic children to more readily assert that their child's otherwise mild exanthem or reaction was a "drug allergy." Without specific skin testing we could not further evaluate these possibilities.

Several clinics have carefully evaluated patients who claim a past penicillin hypersensitivity. Using skin tests with major and minor penicillin antigens, they have shown that from 9% to 19% will actually show evidence of allergic sensitivity.[5,10-12] Therefore, we assume that most of the children in our study are claiming an allergic sensitivity to the penicillins unnecessarily. While the history of their reaction is somewhat helpful, without confirmation by skin tests it is difficult to identify the truly allergic patients.

We have shown that the children who claim a prior penicillin hypersensitivity are more likely to seek medical care and to receive antibiotics. Their antibiotic costs were increased nearly threefold over the control group. They probably represent a sicker subset of children who more frequently require antibiotics for acquired infections. It has not been shown that these excess antibiotic costs could be decreased by more clearly evaluating their claim of penicillin allergy. A recent report by VanArsdel and co-workers suggests that routine penicillin skin testing could be safely and effectively used to determine if patients with a history suggesting penicillin allergy are no longer allergic, if they ever were.[13] Before recommending routine penicillin skin testing for this group, we would suggest more careful study of the potential costs and benefits of this approach.

It is disconcerting that only 59% of those claiming a penicillin hypersensitivity in our questionnaire had it confirmed in their medical records. We compared this finding with a review of coronary care unit charts for adequacy of drug allergy documentation. In that study, only 40% of the charts had documentation of the allergy history.[14] As in our survey, this failure to document drug allergy status occurred even though the information was usually available. The failure to document a drug allergy usually results from one of three causes: failure of a patient to confirm the sensitivity when casually questioned, failure of a physician or pharmacist to ask about previous drug reactions and failure to document the information in a conspicuous area of the chart. We feel that we had a higher proportion of positive histories with the allergy questionnaire because we used several questions to prompt information about prior allergic reactions.

We were also concerned that some patients who claimed a sensitivity in our survey had received penicillins during the two-year interval of observation. Not surprisingly, none of these patients had confirmation of a prior penicillin sensitivity in their charts. Fortunately, no serious adverse reactions occurred, most likely reflecting the very low prevalence of true penicillin allergy in this group. Nevertheless, as long as drug allergy documentation is inadequate, the potential exists for a serious reaction.

When prescribing antibiotics, physicians, nurses and pharmacists should routinely ask patients if they have previously received the drug and whether they had specific adverse effects. If they claim an adverse reaction, the drug should be avoided and a suitable alternative used. To prevent future penicillin reactions, it is essential to clearly

document any claims of prior sensitivities in a visible, conspicuous area of the medical chart.

At this time, patients who claim penicillin hypersensitivity should receive skin testing only if clinical judgment dictates that the alternative antibiotics would be ineffective or potentially more toxic. The major determinant skin test antigens are available as benzyl penicilloyl-polylysine (Pre-Pen; Kremers-Urban Company), but the minor determinant mixture awaits further testing before licensure.[15] Until it is available, fresh penicillin G should be used. The skin testing confers a slight risk of an allergic reaction, so should be done only in a setting where appropriate emergency precautions are present. It should be interpreted by a person skilled in evaluating prick and intradermal skin tests. If penicillin skin tests are positive and there is still no alternative agent available, the patient should be cautiously desensitized to the penicillins. Several protocols have been used for desensitization.[11,16-18] If the skin tests are negative, a low-dose penicillin should be given orally. If tolerated, the full therapeutic dose may then be given.

#### REFERENCES


1. Mathews KP: Clinical spectrum of allergic and pseudoallergic drug reactions. J Allergy Clin Immunol 1984; 74:558-566

2. Orange RP, Donsky GJ: Anaphylaxis, *In* Middleton E Jr, Reed CE, Ellis EF (Eds): Allergy: Principles and Practice. St Louis, CV Mosby, 1978, pp 563-573

3. Valentine M, Chair: Allergic emergencies, *In* NIAID Task Force Report: Asthma and Other Allergic Diseases, US Dept Health, Education and Welfare publication No. (NIH) 79-387. National Institute of Allergy and Infectious Diseases, May 1979, p 501

4. Mendelson LM, Ressler C, Rosen JP, et al: Routine elective penicillin allergy skin testing in children and adolescents: Study of sensitization. J Allergy Clin Immunol 1984; 73:76-81

5. Idsoe O, Guthe T, Willcox RR, et al: Nature and extent of penicillin side-reactions, with particular reference to fatalities from anaphylactic shock. Bull WHO 1968; 38:159-188

6. Green GR, Rosenblum A: Report of the Penicillin Study Group—American Academy of Allergy. J Allergy Clin Immunol 1971; 48:331-343

7. Stember RH, Levine BB: Prevalence of allergic diseases, penicillin hypersensitivity and aeroallergen hypersensitivity in various populations (Abstr 46). J Allergy Clin Immunol 1973; 51:100

8. Kern RA, Wimberley NA Jr: Penicillin reactions, their nature, growing importance, recognition, management, and prevention. Am J Med Sci 1953; 226:357-370

9. Rajka G, Skog E: On the relation between drug allergy and atopy. Acta Allergol 1965; 20:387-395

10. Chandra RK, Joglekar SA, Thomas E: Penicillin allergy: Anti-penicillin IgE antibodies and immediate hypersensitivity skin reactions employing major and minor determinants of penicillin. Arch Dis Child 1980; 55:857-860

11. Bierman CW, VanArsdel PP Jr: Penicillin allergy in children: The role of immunological tests in its diagnosis. J Allergy Clin Immunol 1969; 43:267-272

12. Warrington RJ, Simons FER, Ho HW, et al: Diagnosis of penicillin allergy by skin testing: The Manitoba experieince. Can Med Assoc J 1978; 118:787-791

13. VanArsdel PP Jr, Martonick GJ, Johnson LE, et al: The value of skin testing for penicillin allergy diagnosis. West J Med 1986; 144:311-314

14. Baigelman W, Cupples LA, Harding J, et al: Documentation of drug allergy in CCU patients. Hosp Pract [Off] 1983; 18:90, 94-96

15. Sogn DD, Casale TB, Condemi JJ, et al: Interim results of the NIAID collaborative clinical trial of skin testing with major and minor penicillin derivatives in hospitalized adults. J Allergy Clin Immunol 1983; 71(Suppl):147

16. Sullivan TJ, Yecies LD, Shatz GS, et al: Desensitization of patients allergic to penicillin using orally administered beta lactam antibiotics. J Allergy Clin Immunol 1983; 69:275-282

17. Gorevic PD, Levine BB: Desensitization of anaphylactic hypersensitivity specific for the penicilloate minor determinant of penicillin and carbenicillin. J Allergy Clin Immunol 1981; 68:267-272

18. Naclerio R, Mizrahi EA, Adkinson NF Jr: Immunologic observations during desensitization and maintenance of clinical tolerance to penicillin. J Allergy Clin Immunol 1983; 71:294-301

# Treatment of Severe Hypertension and Hypertensive Crises With Nifedipine

MARK C. HOUSTON, MD, *Nashville, Tennessee*

*The calcium channel blocker nifedipine is an effective antihypertensive agent for the treatment of severe hypertension and hypertensive crises. It produces a prompt, predictable and consistent reduction in systemic arterial pressure with minimal adverse effects. The blood pressure reduction is inversely correlated with the pretreatment blood pressure level. Various nonparenteral administration forms—oral, sublingual, buccal and rectal—permit a versatile, noninvasive, cost-effective alternative to parenteral antihypertensive therapy and continuous hemodynamic monitoring. Blood pressure is reduced to the goal level in 98% of patients with a 10- to 20-mg dose of nifedipine. Hemodynamic changes are favorable and morbidity is uncommon.*

(Houston MC: Treatment of severe hypertension and hypertensive crises with nifedipine. West J Med 1987 Jun; 146:701-704)

Evidence is accumulating that nifedipine, a calcium channel blocker of the dihydropyridine class, is efficacious in treating chronic essential hypertension, severe hypertension and hypertensive crises as well as angina pectoris (vasospastic and obstructive). These clinical uses of nifedipine have been recently reviewed.[1-3] Numerous studies have assessed the clinical use of nifedipine (oral, sublingual, buccal and rectal) in severe hypertension and in hypertensive crises (Table 1).[4-24] Nifedipine produces a prompt, consistent and predictable fall in systemic arterial pressure following a single dose when given by any of these administration routes. In this article I review the use of nifedipine in these clinical situations.

## Definition of Hypertensive Crises and Severe Hypertension

A hypertensive crisis or hypertensive emergency is associated with high intra-arterial blood pressure (diastolic blood pressure above 120 of mercury) and obvious end-organ damage (fundus of eye, brain, heart, kidneys). Both the rate of rise and the absolute level of blood pressure (BP) are important determinants of a hypertensive crisis. These patients are in immediate danger of a catastrophic cardiovascular event, and expeditious but cautious reduction of the BP to a safe level (diastolic BP 100 to 110 mm of mercury) should be accomplished within minutes to an hour.

On the other hand, severe hypertension or a hypertensive urgency often presents with the same diastolic BP elevation (above 120 mm of mercury) but there is little or no end-organ damage, there is less chance of immediate cardiovascular damage, invasive monitoring is not required and the BP can be reduced over a period of 24 hours to a safe level.

Preserving vital organ perfusion with a controlled, cautious BP reduction to a "safe" (diastolic BP of 100 to 110 mm of mercury) but not necessarily "normal" level without inducing side effects should be the primary goal of any antihypertensive regimen.

## Clinical Studies of Nifedipine in Hypertensive Crises and Severe Hypertension

Several hundred patients have been treated for severe hypertension or hypertensive crises with oral, sublingual, buccal or rectal administration of nifedipine (Table 1)[4-24] since Aoki and co-workers first showed its efficacy in 19 patients with hypertensive emergencies who were given a 10- to 30-mg dose of nifedipine sublingually.[6] Pooled data from numerous studies indicate that nifedipine produces a prompt reduction in systolic blood pressure, diastolic blood pressure and mean arterial pressure[5-24] by about 25% below base line in 98% of cases and to the target blood pressure—diastolic BP <90 to 95 mm of mercury—with repeated doses in 95% of patients. The fall in BP is due to a sharp reduction in systemic vascular resistance that is inversely proportional to the initial systemic vascular resistance and blood pressure.[7-10,14,15,19,25-27] There is usually no change in BP or heart rate in normotensive patients. This potent arterial vasodilation results in a reflexive increase in the heart rate in most patients, depending on their predrug heart rate and the presence or absence of congestive heart failure,* which returns to base line before the disappearance of the antihypertensive effect and with ongoing therapy. Other studies have shown no change in the heart rate[13,19] or an actual decrease.[22,23] The change in the heart rate may be inversely proportional to a patient's age.[15] The reduced systemic vascular resistance and reduced impedance to left ventricular function also result in an increased stroke volume,[7,8,10,14,25] cardiac index[7,8,10,14,17,19] and cardiac output.[7,8,10,14,17,19] Myocardial oxygen consumption is reduced, and coronary artery blood flow increases as coronary artery resistance falls.[7,10] The right atrial pressure is usually decreased or unchanged, indicating there is little venous pooling or change on capacitance vessels.[8,17] Pulmonary artery pressure, pulmonary vascular resistance and pulmonary wedge pressure are all re-

*References 4, 6-8, 10-12, 14, 15, 17-20, 24-28.

From the Division of General Internal Medicine, Medical Intensive Care Unit, Cooperative Care Center, Vanderbilt University Medical Center, Nashville, Tennessee. Reprint requests to Mark C. Houston, MD, Room S-1125, Vanderbilt Medical Center N, Nashville, TN 37232.

duced,[8,17,19] and pulmonary edema is usually alleviated. All of these changes induce a favorable hemodynamic and an excellent clinical result that usually relieves congestive heart failure, left ventricular dysfunction, angina pectoris and pulmonary edema.[8,16,17,19]

Nifedipine usually improves renal hemodynamics. The glomerular filtration rate, renal blood flow and renal plasma flow increase,[28] while renal vascular resistance falls. For initial treatment, nifedipine has a natriuretic, diuretic and uricosuric effect.[28] Long-term administration may result in edema and mild volume retention, although this is not a consistent problem.[10,29,30] The edema is usually due to arterial vasodilation without venous vasodilation, effects that could increase the capillary BP and result in edema. In rare cases, nifedipine can cause a transient reversible renal failure in a hypertensive patient with preexisting renal insufficiency.[31]

The dose and method of administration determine the antihypertensive response, time of onset and peak action in a hypertensive crisis. Nifedipine is usually administered as a 10- to 20-mg dose by the sublingual,* oral,[4,8,9,12,14-18,21] buccal[5] or rectal[9] route. The onset of action is the most rapid with sublingual and buccal administration (5 to 10 minutes),[6-10] with oral and rectal administration taking 15 to 30 minutes due to a slower absorption. Peak effect occurs in 20 to 30 minutes.[4-10,13-15,18,24] The duration of action is four to six hours and usually is not affected by the method of administration (Table 1).[4-8,10,24]

There appears to be a plateau effect on BP at a 30-mg dose given within an hour.[10] Nifedipine has been effective and safe in the treatment of children with hypertensive emergencies.[24]

Several factors that may contribute to a rapid hypotensive effect of nifedipine include hypovolemia,[15] age (elderly), the presence of coronary artery disease and the use of prazosin, α-blockers or other vasodilators. Hypotension is apparently rare, however, if nifedipine is used alone. Lower doses are probably advisable when any of the above factors are present (Table 1). The risk for an abrupt and uncontrolled reduction in

*References 6-11, 13, 16, 17, 19, 20, 22-24.

TABLE 1.—*Suggested Regimens for Administering Nifedipine in Patients With Hypertensive Emergency and Urgency*

| *Clinical Features* | *Loading Dose, mg* | *Maintenance Dose, mg* |
|---|---|---|
| Diastolic blood pressure >130 mm of mercury | 20 PO, buccal or sublingual | 10 every 30 min until target BP is reached |
| Diastolic blood pressure 115 to 130 mm of mercury | 10 PO, buccal or sublingual | 5 to 10 every 30 min until target BP is reached |
| Diastolic blood pressure <115 mm of mercury | 5 to 10 PO, buccal or sublingual | 5 every 30 min until target BP is reached |
| Patient characteristics | 5 PO, buccal or sublingual | 5 every 30 min until target BP is reached |
| Elderly (age >65 years); history of coronary artery disease; history of cerebrovascular accident; volume depletion; concomitant antihypertensive agent | | |

BP=blood pressure, PO=by mouth

TABLE 2.—*Summary of Reported Studies of Nifedipine Administration in Cases of Hypertensive Crisis or Severe Hypertension*

| *Author, Reference* | *Patient, number* | *Mean Age, years* | *MĀP Before/After, mm of mercury* | *Systolic BP Before/After, mm of mercury* | *Diastolic BP Before/After, mm of mercury* | *Pulse Before/After, beats/min* | *Dose, mg, and Route* | *Response Maximum, min* |
|---|---|---|---|---|---|---|---|---|
| Given et al, 1985[16] | 9 | 65.0 | 140/103 | 211/153 | 105/78 | Not stated | 10-20 oral, SL | 30-60 |
| Evans et al, 1984[4] | 10 | 51.2 | 142/104 | 202/143 | 113/84 | 66/71 | 10 oral | 30.0 |
| Haft and Litterer, 1984[5]* | A-42 | 58.6 | 154/112 | 205/158 | 128/89 | Not stated | 10 buccal | 39.9 |
| | B-19 | 48.2 | 156/117 | 212/165 | 128/94 | Not stated | 20 buccal | 66.0 |
| Bertel et al, 1983[15] | 25 | Not stated Range 37-80 | 158/110 | 221/152 | 126/89 | 74/84 | 10-20 oral | 30.0 |
| Dilmen et al, 1983[24] | 21 | 11.3 | 152/109 | 181/132 | 136/98 | 108/117 | 0.25-0.50/kg SL | 30.0 |
| Erbel et al, 1983[22] | 30 | 66.0 | 160/117 | 235/170 | 123/91 | 95/83 | 20 SL | 20.0 |
| Huysmans et al, 1983[20] | 10 | ... | 163/129 | 221/172 | 134/107 | 83/98 | 10-20 SL | 30.0 |
| Lacche and Bagaglia, 1983[23] | 40 | 70.0 | 159/114 | 232/168 | 122/87 | 99/86 | 20 SL | 30-45 |
| Conen et al, 1982[18] | 18 | 64.0 | 154/107 | 220/150 | 122/86 | 74/85 | 20 oral | 20-30 |
| Magometschnigg, 1982[21] | 17 | 58.0 | 193/126 | 260/178 | 160/100 | 78/84 | 20 oral | 30-45 |
| Beer et al, 1981[7]* | A-17 | 43.0 | 130/105 | 172/140 | 109/88 | 79/84 | 10 SL | 20.0 |
| | B-26 | 46.0 | 153/118 | 204/160 | 128/97 | 76/89 | 20 SL | 20.0 |
| Takekoshi et al, 1981[9] | 16 | 57.7 | 159/115 | 227/163 | 125/92 | ... | 5-10 oral | 50.0 |
| | | | | | | | 3-10 SL | 15-25 |
| | | | | | | | 5-20 rectal | 40-50 |
| Imai et al, 1980[12] | 9 | 42.2 | 159/122 | 216/166 | 130/95 | ↑30 | 20 oral | 60.0 |
| Olivari et al, 1979[14] | 27 | 52.0 | 145/114 | ↓21% | ↓19% | ↑17% | 10 oral | 30.0 |
| Polese et al, 1979[19] | 7 | 49.0 | 154/122 | 221/177 | 120/94 | 88/96 | 10 SL | 30-35 |
| Aoki et al, 1978[10] | 10 | 46.0 | 133/102 | 173/130 | 113/87 | 66/80 | 10 SL | 15-20 |
| Bartorelli et al, 1978[17] | 36 | 54.0 | 140/112 | Not stated | Not stated | 75/88 | 10 oral, SL | 20-30 |
| Kuwajima et al, 1978[13] | 6 | 66.0 | 152/104 | 236/162 | 110/75 | Not stated | 10 SL | 30.0 |
| Pederson and Mikkelsen, 1978[11] | 17 | 46.0 | 135/121 | 175/159 | 115/102 | ↑15 | 10-20 SL | 35.0 |
| Guazzi et al, 1977[8]* | A-17 | 54.0 | 150/114 | Not stated | Not stated | 76/86 | 10 oral | 30.0 |
| | B-9 | 54.0 | 150/114 | Not stated | Not stated | 76/86 | 10 SL | 15.0 |
| Aoki et al, 1976[6] | 19 | 47.0 | 131/94 | 177/123 | 108/80 | 73/85 | 30 SL | 15.0 |

BP=blood pressure, MĀP=mean arterial pressure, SL=sublingual

*The patients in this study were divided into 2 groups of differing dosages or routes of administration.

BP has the potential to impair the cerebral circulation and induce cerebral dysfunction, retinal ischemia or cerebrovascular accident (see below). The judicious use of nifedipine is particularly crucial in patients with chronic severe hypertensive disease.

A total of 459 patients with severe hypertension or hypertensive emergencies treated with nifedipine has been reported to date (Table 2). The pooled average reduction in systolic BP is 24% (range 10% to 40%), diastolic BP 25% (range 12% to 38%), mean arterial pressure 24% (range 10% to 39%) and increase in heart rate is 15%. The maximum antihypertensive effect for a 10- to 20-mg dose of nifedipine using the sublingual, oral or buccal route is 15 minutes, 30 minutes and 40 minutes, respectively, with a duration of action of three to five hours. All available dosage forms appear to have similar efficacy.

## Adverse Effects

The side effects attributed to nifedipine in the short- and long-term treatment of hypertension have been well described.[24,25] These include headache in 4%,[6,8,10,26] palpitations in 5%,[6,8,10,26] premature ventricular beats in 4%,[8] facial burning in 6%,[8] leg paresthesias in 6%,[8] flushing or hot flashes in 5%,[6,7,10,25] giddiness,[10] hypotension[7] and pedal edema in 2% to 3%,[26,29,30] fluid retention in 3%[26,29,30] and fatigue[4] and dry mouth in 1%.[25] Most of these side effects resolve with long-term therapy, particularly if combined with other agents such as central $\alpha$-agonists or $\beta$-blockers,[24,25] and do not require cessation of therapy. Acute, reversible renal failure may occur in some patients with chronic renal failure.[31] Specific drug interactions with other antihypertensive agents, particularly $\beta$-blockers, could result in hypotension or a possible reduction in cardiac output and congestive heart failure. Hypotension is very uncommon, however, with nifedipine monotherapy.

## Combination Antihypertensive Therapy With Nifedipine

The addition of nifedipine with propranolol hydrochloride,[2,29,30,32,33] methyldopa,[2,32,34] clonidine,[2,12] diuretics[2,32,33] or other antihypertensive drugs enhances the antihypertensive effect and reduces volume retention, heart rate and plasma renin activity in both short- and long-term treatment of hypertension. Nifedipine has been used as monotherapy for hypertension.[35] Its effectiveness is not usually limited by reflexive volume retention.[29,30] Nifedipine appears to be most effective in the elderly, those with a higher BP and those with low plasma renin activity[2,27,36] when administered on a long-term basis, whereas these factors are not important in an acute hypertensive emergency except for the level of BP. The role of calcium antagonists in the treatment of hypertension has been reviewed recently.[37,38]

Although other calcium blockers such as diltiazem and verapamil have been used in cases of severe hypertension and hypertensive crises and may be equally effective, nifedipine is much easier to administer and does not reduce cardiac output or slow atrioventricular conduction, which occurs with the use of verapamil and to a lesser extent with diltiazem.[37,38]

## Regional Blood Flow in Hypertensive Emergencies

As BP is reduced in patients with severe hypertension, it is important to assess the relative effect on regional and global blood flow to vital organs, such as the central nervous system, kidneys and myocardium. Unfortunately, the effect of lowering the BP on these various organs has not been well studied. Until recently, the ability to assess cerebral blood flow (global and regional) has been limited by the technical methods used. Newer techniques using single photon emission tomography and xenon 133 may allow better, although not optimal, interpretation of the effects of a rapid reduction in systemic arterial pressure on the cerebral blood flow.[15,39,40] It appears that the lower-limit mean arterial pressure for cerebral blood flow autoregulation in a patient with chronic hypertension is set much higher (120 to 160 mm of mercury) than in patients with acute hypertension (60 to 120 mm of mercury) or in those with a normal BP. Theoretically, rapid reductions in BP below this level could decrease the cerebral blood flow to critical levels and precipitate a cerebrovascular accident or other symptoms and signs of cerebral hypoperfusion.[40]

Autoregulation of cerebral blood flow in patients with chronic hypertension and those with normal BP is unimpaired until the mean arterial pressure is reduced by 25% to 30% or the absolute lower limit of blood pressure autoregulation is reached, whichever occurs first.[41,42] Neurologic complications usually do not occur if BP is maintained above these levels. If the mean arterial pressure falls 40% or more below the initial BP, however, then definite neurologic symptoms and complications will occur.[41,42] The potential advantages and disadvantages of the use of nifedipine in hypertensive crises are summarized in Table 3.

## Conclusions

Nifedipine administered orally, sublingually, buccally or rectally in patients with hypertensive urgency and emergency or severe hypertension produces a prompt (minutes), consistent (98%), predictable (25% average reduction), dose-re-

TABLE 3.—*Potential Advantages and Disadvantages of the Use of Nifedipine in Hypertensive Crises*

| |
|---|
| Advantages |
| The mean arterial pressure is reduced proportionally to the level of the pretreatment blood pressure and systemic vascular resistance. The degree of reduction averages 25% and is rapid and consistent |
| Admission to hospital and hemodynamic monitoring are not always required for a hypertensive urgency, but are warranted in a hypertensive crisis |
| Reflex tachycardia is common, but angina and myocardial infarction are rare. Coronary artery dilation and a favorable balance of myocardial oxygen supply and demand occur |
| Left ventricular impedance is decreased, which improves signs and symptoms of congestive heart failure |
| The numerous dosage forms all have equal efficacy without the need for parenteral administration |
| The duration of antihypertensive effect is 3 to 6 hours following each dose |
| Side effects are minor but frequent |
| Disadvantages |
| Potential hypotension or normalization of blood pressure too rapidly may reduce regional or global perfusion to some vital organs and cause complications |
| Acute reversible renal failure has been reported in patients with chronic renal insufficiency and a hypertensive crisis if treated with nifedipine |
| Hypertensive encephalopathy and cerebral edema may theoretically be exacerbated |
| A precipitous fall in blood pressure may occur when nifedipine is given to patients on a regimen of $\alpha$-blockers, prazosin or another vasodilator, or those who have hypovolemia* |

*From Bertel et al.[15]

lated and safe reduction in systemic arterial pressure with few adverse effects and a duration of action of three to six hours. The fall in blood pressure is inversely correlated with the pretreatment mean arterial pressure and systemic vascular resistance, but is independent of age, sex, race or plasma renin activity during the short-term treatment. The overall hemodynamic effects are favorable with an increase in cardiac output, cardiac index, stroke volume, glomerular filtration rate, renal blood flow, renal plasma flow, cerebral blood flow and coronary artery blood flow and a decrease in systemic vascular resistance, pulmonary vascular resistance, pulmonary artery pressure and pulmonary wedge pressure. Although the heart rate is increased in most, myocardial ischemic syndromes are rare due to an overall favorable balance in myocardial oxygen supply and demand. These hemodynamic changes, in conjunction with the fall in BP, do not usually induce any significant clinical problems, and no deaths have occurred in the 459 patients studied to date. Precautions should be taken, however, particularly in the elderly and patients with hypovolemia, chronic renal failure, coronary artery disease, cerebrovascular disease or hypertensive encephalopathy in not reducing the BP too precipitously or below the lower limit of autoregulation for the brain, heart, kidneys or other vital organs. A rapid reduction to normal levels may not be desirable within the first 24 to 48 hours in many patients with a hypertensive emergency. The ability to predict an approximate 25% reduction in systolic and diastolic BP and mean arterial pressure with a 10-mg dose will assist clinicians in selecting the appropriate patients for this method of treating hypertensive crises. It should be emphasized, however, that the use of nifedipine does not allow a cautious, controlled, slow reduction in BP, but rather causes a dramatically rapid fall that could possibly cause problems in some patients.

Nifedipine may be particularly useful in the subset of patients with angina or congestive heart failure and a hypertensive crisis. Nonparenteral administration of nifedipine is simple, efficacious, cost-effective and reduces the need for invasive hemodynamic monitoring and often the need for hospital admission. Hospital admissions and monitoring are mandatory in patients with a hypertensive emergency, but for a hypertensive urgency, outpatient treatment may be appropriate if one remembers that a good initial response in a high percentage of patients treated for a short period requires careful observation for several hours before discharge. Patients should then be seen within 12 to 24 hours for adjustment of antihypertensive therapy.

Nifedipine is effective and safe in the treatment of chronic hypertension as a single agent or in combination with a diuretic, central $\alpha$-agent, $\beta$-blocker or other antihypertensive drugs.[26-28,30,37,38] Calcium blockers appear to be most effective in the long-term treatment of elderly black patients with low renin activity and volume-dependent hypertension. The time of onset and maximum effect but not the duration of the antihypertensive effect depend on the method of administration. The clinical use of nifedipine in these patients is very promising, but more prospective studies are necessary to compare it with other approved emergency antihypertensive regimens.

#### REFERENCES


1. Schwab MC, Singh BH: Nifedipine: Pharmacologic properties and clinical use. Hosp Formulary 1985; 20:85-98
2. Spivak C, Ocken S, Frishman WH: Calcium antagonists: Clinical use in the treatment of systemic hypertension. Drugs 1983; 25:154-177
3. Frishman WH, Weinberg P, Peled HB, et al: Calcium entry blockers for the treatment of severe hypertension and hypertensive crises. Am J Med 1984; 77:35-45
4. Evans MG, Olanoff LS, Hurwitz G, et al: Use of nifedipine as an adjunct to current antihypertensive therapy. Arch Intern Med 1984; 144:985-987
5. Haft JI, Litterer WE: Chewing nifedipine to rapidly treat hypertension. Arch Intern Med 1984; 144:2357-2359
6. Aoki K, Yoshida T, Kato S, et al: Hypotensive action and increased plasma renin activity by $Ca^{2+}$ antagonist (nifedipine) in hypertensive patients. Jpn Heart J 1976; 17:479-484
7. Beer N, Gallegos I, Cohen A, et al: Efficacy of sublingual nifedipine in the acute treatment of systemic hypertension. Chest 1981; 79:571-574
8. Guazzi M, Olivari MT, Polese A, et al: Nifedipine, a new antihypertensive with rapid action. Clin Pharmacol Ther 1977; 22:528-532
9. Takekoshi N, Murakami E, Murakami H, et al: Treatment of severe hypertension and hypertensive emergency with nifedipine, a calcium antagonistic agent. Jpn Circ J 1981; 45:852-860
10. Aoki K, Kondo S, Mochizuki A, et al: Antihypertensive effect of cardiovascular $Ca^{2+}$ antagonist in hypertensive patients in the absence and presence of beta-adrenergic blockade. Am Heart J 1978; 96:218-226
11. Pederson OL, Mikkelsen E: Acute and chronic effects of nifedipine in arterial hypertension. Eur J Clin Pharmacol 1978; 14:375-381
12. Imai Y, Abe K, Otsuka Y, et al: Management of severe hypertension with nifedipine in combination with clonidine or propranolol. Arzneimittelforsch 1980; 30:674-678
13. Kuwajima I, Ueda K, Kamata C, et al: A study on the effects of nifedipine in hypertensive crises and severe hypertension. Jpn Heart J 1978; 19:455-467
14. Olivari MT, Bartorelli C, Polese A, et al: Treatment of hypertension with nifedipine, a calcium antagonist agent. Circulation 1979; 59:1056-1062
15. Bertel O, Conen D, Radu EW, et al: Nifedipine in hypertensive emergencies. Br Med J 1983; 286:19-21
16. Given BD, Lee TH, Stone PH, et al: Nifedipine in severely hypertensive patients with congestive heart failure and preserved ventricular systolic function. Arch Intern Med 1985; 145:281-285
17. Bartorelli C, Magrini F, Moruzzi P, et al: Haemodynamic effects of a calcium antagonist agent (nifedipine) in hypertension: Therapeutic implications. Clin Sci 1978; 55:291S-292S
18. Conen D, Bertel O, Dupach UC: An oral calcium antagonist for treatment of hypertensive emergencies. J Cardiovasc Pharmacol 1982; 4(Suppl): S378-S382
19. Polese A, Fiorentini C, Olivari MT, et al: Clinical use of a calcium antagonist agent (nifedipine) in acute pulmonary edema. Am J Med 1979; 66:825-830
20. Huysmans FTM, Sluiter HE, Thien TA, et al: Acute treatment of hypertensive crisis with nifedipine. Br J Clin Pharmacol 1983; 16:725-727
21. Magometschnigg D: Acute hypotensive response to nifedipine. Dtsch Med Wochenschr 1982; 107:1423-1428
22. Erbel R, Meyer J, Brand E, et al: Emergency treatment of hypertensive crisis with sublingual nifedipine. Postgrad Med J 1983; 59(suppl 3):134-136
23. Lacche A, Bagaglia P: Hypertensive emergencies: Effects of therapy by nifedipine administered sublingually. Curr Ther Res 1983; 34:879-887
24. Dilmen U, Cağlar MK, Senses DA, et al: Nifedipine in hypertensive emergencies of children. Am J Dis Child 1983; 137:1162-1165
25. Murakami M, Murakami E, Takekoshi N, et al: Antihypertensive effect of (4-2′-nitrophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarbonic acid dimethylester (Nifedipine, Bay-a 1040), a new coronary dilator. Jpn Heart J 1972; 13:128-135
26. Frishman WH, Charlap S: Nifedipine in the treatment of systemic hypertension. Arch Intern Med 1984; 144:2335-2336
27. Klowski W, Bertel O, Erne P: Hemodynamic and reflex responses to acute and chronic antihypertensive therapy with the calcium entry blocker nifedipine. Hypertension 1983; 5(suppl I):I70-I74
28. Pederson OL: Calcium blockade in arterial hypertension. Hypertension 1983; 5(suppl II):II74-II79
29. Pederson OL, Christensen CK, Mikkelsen E, et al: Relationship between the antihypertensive effect and steady-state plasma concentration of nifedipine given alone or in combination with a beta-adrenoceptor blocking agent. Eur J Clin Pharmacol 1980; 18:287-293
30. Husted SE, Nielson K, Christensen CK, et al: Long term therapy of arterial hypertension with nifedipine given alone or in combination with a beta-adrenocepter blocking agent. Eur J Clin Pharmacol 1982; 22:101-103
31. Diamond JR, Cheung JY, Fang LST: Nifedipine-induced renal dysfunction. Am J Med 1984; 77:905-909
32. Bayley S, Dobbs RJ, Robinson BF: Nifedipine in the tratment of hypertension: Report of a double-blind controlled trial. Br J Clin Pharmacol 1982; 14:509-512
33. Dean S, Kendall MJ: Nifedipine in the treatment of difficult hypertensives. Eur J Clin Pharmacol 1983; 24:1-5
34. Guazzi MD, Fiorentini C, Olivari MT, et al: Short and long term efficacy of a calcium-antagonist agent (nifedipine) combined with methyldopa in the treatment of severe hypertension. Circulation 1980; 61:913-919
35. Hornung RS, Gould BA, Jones RI: Nifedipine tablets for systemic hypertension: A study using continuous ambulatory intra-arterial recording. Am J Cardiol 1983; 51:1323-1327
36. Erne P, Bolli P, Bertel O, et al: Factors influencing the hypotensive effects of calcium antagonists. Hypertension 1983; 5(suppl II):II97-II102
37. Guazzi MD, Polese A, Fiorentini C, et al: Treatment of hypertension with calcium antagonists: Review. Hypertension 1983; 5(suppl II):II85-II90
38. Frohlich ED: Calcium channel blockers: A new dimension in antihypertensive therapy. Am J Med 1984; 77:1-45
39. Tamaki K, Sadoshima S, Baumbach GL, et al: Evidence that disruption of the blood-brain barrier precedes reduction in cerebral blood flow in hypertensive encephalopathy. Hypertension 1984; 6(suppl I):I75-I81
40. Olsen TS: Should induced hypertension or hypotension ever be used in the treatment of stroke? Acta Med Scand [Suppl] 1983; 678:113-120
41. Harden R, Russell R: Iatrogenically induced hypertensive encephalopathy. Johns Hopkins Med J 1979; 145:44-48
42. Strandgaard S, Paulson OB: Cerebral autoregulation. Stroke 1984; 15:413-415

Medical Progress

# Treatable Dementias

MICHAEL E. MAHLER, MD; JEFFREY L. CUMMINGS, MD, *and* D. FRANK BENSON, MD, *Los Angeles*

*Dementia is an acquired impairment of intellect produced by brain dysfunction. In the past, dementia was regarded as inevitably chronic, progressive and irreversible. More recently dementia has been viewed as a clinical syndrome that may be produced by both irreversible and reversible conditions. Recognition of the presence of a dementia syndrome should be followed by an evaluation for potentially treatable causes of the intellectual deterioration. Dementia treatment includes therapy for reversible or curable dementias and nonspecific interventions that may improve the condition of patients with progressive dementia syndromes.*

(Mahler ME, Cummings JL, Benson DF: Treatable dementias. West J Med 1987 Jun; 146:705-712)

Dementia is defined as an acquired, persistent impairment of intellectual function with deficits in at least three of the following five spheres of mental activity: memory, language, visuospatial skills, cognition (abstraction, mathematics, judgment and so forth) and personality.[1] This definition distinguishes dementia from conditions in which the deficit is limited to a single neuropsychological domain such as memory or language as in amnesia or aphasia, respectively. It also contrasts dementia with acute confusional states (delirium), which are characterized by an abrupt onset, brief duration of hours to days and predominantly attentional deficits. (Confusional states lasting weeks to months are properly classified as dementias.) Dementia is also distinguished from mental retardation where the deficits are congenital rather than acquired in origin. Dementia, using this definition, is a clinical syndrome that may result from many different disease processes that interfere with brain function to compromise intellectual abilities.

In the United States, the size of the population over age 65 will increase from 22 million in 1978 to 51 million in 2030, and 5% to 15% of these persons will have a dementia syndrome.[2] The inevitable growth in the prevalence of dementia is accompanied by the need for expensive medical and social services, hospital and nursing home beds, day care facilities and prescription medications. The increasing size of the elderly population and the concomitant increase in the number of patients with dementia has made the search for treatable causes of the syndrome more imperative.[3]

The precise frequency of treatable dementia has been difficult to determine because of the different referral sources, research methods and definitions of dementia used in investigating the causes of dementia. Cummings and Benson reviewed seven case series in which the causes of dementia had been reported.[4] They found that potentially reversible dementias included metabolic disorders (0% to 17%), obstructive hydrocephalus (1% to 8%), infections (1% to 4%), toxic conditions (1% to 8%), subdural hematomas (1% to 2%) and cerebral neoplasms (1% to 8%). Thus, between 5% and 47% of patients referred with a diagnosis of dementia had a potentially reversible structural, toxic or metabolic condition. An additional 2% to 28% of patients had treatable psychiatric disorders, primarily depression, accounting for their intellectual impairment. Of the remaining patients, 30% to 40% had treatable if not reversible conditions such as multi-infarct dementia, alcoholic dementia and progressive extrapyramidal syndromes with dementia, such as Parkinson's disease and Huntington's disease. Chronic progressive disorders such as Alzheimer's disease affected 25% to 50% of patients.

An emphasis on detecting and ameliorating treatable causes of intellectual impairment applies to all patients with dementia. In some cases a completely curable disorder such as hypothyroidism or vitamin $B_{12}$ deficiency may be discovered. In others, such as neurosyphilis or multi-infarct dementia, intervention may modify the course of the illness, sparing a patient further deterioration without reversing existing deficits. Treatment may lessen related symptoms without altering the intellectual difficulty, as in Huntington's disease. Even in chronic, progressive dementias, such as Alzheimer's disease, evaluation may reveal treatable complications such as electrolyte imbalances, pulmonary and urinary tract infections or drug toxicities that may be exacerbating the mental state and behavioral changes.[5]

A potential criticism of an emphasis on reversible dementias is that, even when a theoretically reversible cause is found, therapy for the underlying cause may not fully restore intellectual function.[5] This is particularly so if the dementia has been present for several years before the cause is discovered. Intervention, however, may halt the progression of mental decline, and treatment may prevent the need for placement in a nursing home, reduce the level of dependence or allow for a higher quality of life.

The evaluation of patients with dementia has been made more rewarding by the development of new technologies. Contemporary clinicians in most areas have access to computed x-ray tomography, magnetic resonance imaging, cisternography, serum drug assays and automated serum metabolic assessments that aid in the discovery of intracranial as well as systemic disorders affecting brain function. At the same time, clinical criteria for the diagnosis of irreversible disorders have been clarified making it more obvious which

From the Department of Neurology, Reed Neurological Research Center, University of California, Los Angeles, School of Medicine, and the Neurobehavior Unit, Veterans Administration Medical Center (Brentwood Division), Los Angeles. This work was supported by the Veterans Administration.

Reprint requests to Michael E. Mahler, MD, Reed Neurological Research Center, 710 Westwood Plaza, Los Angeles, CA 90024.

TABLE 1.—*Reversible Dementias*

| *Disorder* | *Clinical Characteristics* | *Treatment* |
|---|---|---|
| ***Intracranial Disorders*** | | |
| Meningioma, low-grade astrocytoma, solitary metastasis | Headache; seizures; papilledema; gradually progressive focal signs | Surgical removal |
| Pituitary adenoma | Visual field deficits; headache; endocrinologic changes | Surgical removal; radiation therapy, or bromocriptine mesylate |
| Hydrocephalus | Dementia; incontinence; gait disturbance | Ventricular shunting |
| Subdural hematoma | Headache; fluctuating course; psychomotor slowing; decreased alertness (may occur without focal signs, without known trauma) | Surgical drainage; antiedema agents |
| Cerebral abscess | Headache; fever; focal signs; multiple CT lesions; CSF leukocytosis, cultures usually negative | High-dose penicillin, chloramphenicol; steroids; surgical aspiration or excision in some cases |
| Tuberculous meningitis | Subacute course; lethargy; fever (may be absent in elderly); stiff neck; CSF: increased lymphocytes, decreased glucose, positive cultures or acid-fast bacilli; tuberculoma mass may occur | Isoniazid, ethambutol HCl, rifampin combination; ventricular shunt if hydrocephalus occurs |
| Cryptococcal meningitis | Immunocompromised host, may have mass lesions; organisms in CSF seen in india ink; CSF antigens | Amphotericin B (intravenous or intrathecal); flucytosine |
| Toxoplasmosis | Immunocompromised host; mass lesions and focal signs; antibody titers | Sulfadiazine and pyrimethamine |
| Cerebral malaria | Stupor; fevers; brain edema; *Plasmodium falciparum* | Quinine (steroid use controversial) |
| Whipple's disease | Constitutional symptoms; malabsorption; uveitis; supranuclear gaze palsy; multiple low-density CT lesions; PAS-positive GI or brain biopsy | Penicillin; tetracycline; chloramphenicol |
| Giant cell arteritis | Headache; vision loss; polymyalgia rheumatica; elevated sedimentation rate (ESR) | Steroids |
| Systemic lupus erythematosus | Neuropsychiatric syndromes; seizures; systemic manifestations | Steroids |
| Cerebral arteritis | Headache; strokelike signs; systemic signs of arteritis; inflammatory CSF; elevated ESR; "beading" arteriogram | Steroids |
| Sarcoidosis | Cerebral mass lesion; may be without pulmonary disease | Steroids |
| ***Systemic Illnesses*** | | |
| Cardiac disease | Heart failure; arrhythmia; other causes of decreased cerebral perfusion; lethargy; chronic confusional state | Diuretics; digoxin; antiarrhythmic agents |
| Hypertensive encephalopathy | Pronounced elevation of blood pressure; headache; retinopathy; nephropathy; seizures | Antihypertension drugs |
| Anemia | Fatigue; lethargy; impaired concentration | Transfusion; correct underlying condition |
| Hyperviscosity syndrome | Polycythemia; Waldenström's macroglobulinemia | Blood removal; plasmapheresis |
| Pulmonary disease | COPD; pneumonia; other causes of chronic hypercapnia or hypoxia; headache; papilledema; tremor; myoclonus | Ventilation; oxygen; correct acidosis if present; treat underlying condition |
| Sleep apnea | Loud snoring; daytime lethargy; nocturnal $O_2$ desaturation, apnea, arrhythmia | Tracheostomy; protriptyline HCl for central type apnea |
| Chronic renal failure | Uremia and other metabolic derangements; fatigue; apathy; irritability; tremor; asterixis; myoclonus; neuropathy; EEG may have paroxysmal slowing | Dialysis; kidney transplantation |
| Hepatic encephalopathy | Liver disease stigmata; asterixis; tremor; myoclonus; hyperammonemia frequent; EEG triphasic waves; exacerbated by diuretics, sedatives, GI tract bleeding, dietary protein | Lactulose; neomycin; reduce dietary protein; correct exacerbating factors |
| Hypernatremia | Usually dehydration; diabetes insipidus | Rehydration; vasopressin snuff |
| Hyponatremia | Weakness; lethargy; seizures; often inappropriate antidiuretic hormone secretion | Fluid restriction |
| Hypercalcemia | Weakness; fatigue; mood changes; increased calcium due to hyperparathyroidism, multiple myeloma, bone metastases, ectopic parathyroid hormone | Hydration and diuretics; plicamycin (mithramycin); treat underlying disorder |
| Hypocalcemia | Tetany; seizures; may result from hypoparathyroidism, renal failure, hypomagnesemia; basal ganglia may calcify with extrapyramidal syndrome | Calcium and vitamin D supplements; phosphate binders |
| Hypomagnesemia | Similar to hypocalcemia; often associated with alcoholism | Magnesium sulfate |
| Hypothyroidism | May present with dementia; signs of myxedema; delayed reflexes; elevated thyroid-stimulating hormone | Thyroid hormone replacement |
| Hyperthyroidism | Restlessness, anxiety; tremor; tachycardia; exophthalmic ophthalmoplegia; may be masked in elderly | Propranolol HCl; propylthiouracil; surgical procedure; radioiodine therapy |
| Cushing's syndrome | Central obesity; striae; hypertension; diabetes mellitus; irritability, depression; exogenous or endogenous corticosteroid excess | Treat underlying cause |
| Addison's disease | Weakness; hypotension; pigment change; hyponatremia; hyperkalemia | Corticosteroid replacement |
| Hyperglycemia | Diabetes mellitus; hyperosmolar state with stupor; may have minor focal signs | Hydration; hypoglycemic agents; diet |
| Hypoglycemia | Excess hypoglycemic agents; chronic or recurrent from insulinoma | Glucose; correct underlying disorder |
| Porphyria | Abdominal pain, GI symptoms; neuropathy; personality change; agitation; confusion | Avoid the use of barbiturates, sulfa drugs, other precipitants |

COPD=chronic obstructive pulmonary disease, CSF=cerebrospinal fluid, CT=computed tomography, EEG=electroencephalogram, GI=gastrointestinal, HCl=hydrochloride, PAS=periodic acid-Schiff

(Continued on Next Page)

patients require more thorough investigations. The diagnosis of Alzheimer's disease, the principal cause of irreversible dementia, now depends on both inclusionary and exclusionary clinical criteria.[6,7] Patients whose symptoms differ significantly from the characteristic syndrome of Alzheimer's disease must be evaluated carefully for potentially reversible dementing disorders, and those diagnosed as having Alzheimer's disease clinically should be evaluated for possible supervening treatable conditions. This reliance on a simultaneous "rule-in/rule-out" approach guides the selection of appropriate laboratory assessments in each case.

Finally, the emphasis on treatable causes of dementia provides a framework capable of including the therapeutic advances of the future. Diseases now viewed as untreatable and irreversible may become reversible with the development of appropriate interventions in the same way that hypothyroidism, neurosyphilis and obstructive hydrocephalus were once irreversible and progressive but are now recognized as treatable causes of dementia.

The treatable dementias are divided below into those that may be completely reversed with timely, appropriate treatment; those in which specific treatment may alter the course of the dementia or provide symptomatic relief, and those in which treatment is limited to preventing secondary complications of the disorder.

## Reversible Dementias

Reversible dementias include a variety of intracranial disorders and a heterogeneous array of metabolic and toxic encephalopathies. Table 1 summarizes these disorders, their principal associated clinical characteristics and the appropriate therapeutic interventions.

### *Intracranial Conditions*

Among the intracranial conditions are mass lesions such as cerebral neoplasms, granulomas, abscesses and gummas. These space-occupying masses often cause focal sensorimotor signs and symptoms. Seizures may result from local destructive effects of the lesions, and lethargy, headache, vomiting and papilledema may be produced by increased intracranial pressure. Symptoms due to surgically resectable meningiomas, low-grade gliomas, solitary metastases and pituitary adenomas are more reversible than those resulting from other more malignant neoplasms.

Obstructive hydrocephalus is a special case of a space-occupying process. Hydrocephalus may be of the noncommun-

(Continued from Previous Page)

TABLE 1.—*Reversible Dementias (Continued)*

| *Disorder* | *Clinical Characteristics* | *Treatment* |
|---|---|---|
| ***Systemic Illnesses (Continued)*** | | |
| Vitamin $B_{12}$ deficiency | Memory loss may precede anemia; myelopathy and neuropathy; pernicious anemia, other GI disorders; positive Schilling's test | Vitamin $B_{12}$ injections |
| Folate deficiency | Syndrome similar to vitamin $B_{12}$ deficiency; alcoholism, malabsorption, phenytoin | Folate supplementation |
| Thiamine (vitamin $B_1$) deficiency | Memory disorder; ophthalmoplegia; ataxia; neuropathy | Thiamine supplementation |
| Niacin deficiency | Pellagra; weakness and lethargy; dermatitis; diarrhea, other GI symptoms | Niacin supplementation |
| ***Toxic Disorders*** | | |
| Major tranquilizers | Chronic confusional state; parkinsonism | Lower dose or discontinue medication |
| Antidepressants | Chronic confusional state; tremors; anticholinergic effects | Lower dose or discontinue medication |
| Sedative-hypnotics | Lethargy, confusional state; withdrawal syndromes | Lower dose or discontinue medication (taper dose) |
| Narcotics | Pupillary constriction; constipation; respiratory depression; elderly sensitive to low doses | Lower dose or discontinue; give naloxone HCl for acute condition |
| Anticholinergics | Memory loss; confusional state; psychosis; dilated pupils; dry skin; tachycardia; wide variety of medications involved | Discontinue medication; give physostigmine in acute state |
| Antihypertensives | Psychomotor slowing, depression; methyldopa, reserpine, clonidine, propranolol use | Switch to other agents for blood pressure control |
| Anticonvulsants | Sedation from barbiturates; phenytoin use may give cerebellar signs; toxic levels | Switch to another drug |
| Digoxin | GI and cardiac side effects; confusional state | Adjust dose |
| Antiparkinsonian | Levodopa, amantadine, bromocriptine use; confusional state; psychosis | Reduce medication dose |
| Antibiotics | Penicillin, chloramphenicol use; high doses, often from decreased clearance in elderly | Adjust dose |
| Gastrointestinal agents | Chronic confusional state; cimetidine use; metaclopramide may cause extrapyramidal syndrome | Adjust or discontinue medication |
| Antineoplastic agents | Asparaginase; intrathecal administration of methotrexate | Discontinue medication |
| Lead | Encephalopathy; motor neuropathy; headache; seizures; anemia; lead lines | Edetate chelation; eliminate exposure |
| Arsenic | Somnolence; sensory neuropathy; GI symptoms; Mees' lines | Chelation; eliminate exposure |
| Organic solvents | Headache; lethargy; poor concentration; peripheral neuropathy | Eliminate exposure |
| Insecticides | Irritability; forgetfulness; organophosphates | Avoid exposure |
| ***Psychiatric Disorder*** | | |
| Depression | Psychomotor retardation; neurovegetative changes; altered mood; prior depression history; may be masked in elderly; may be associated with other illnesses or drugs | Psychotherapy; antidepressants; electroconvulsive therapy |

COPD=chronic obstructive pulmonary disease, CSF=cerebrospinal fluid, CT=computed tomography, EEG=electroencephalogram, GI=gastrointestinal, HCl=hydrochloride, PAS=periodic acid-Schiff

TABLE 2.—*Features That Distinguish Between Toxic-Metabolic Dementias and Alzheimer's Disease*

| *Feature* | *Toxic-Metabolic Dementia* | *Alzheimer's Disease* |
|---|---|---|
| History | | |
| Onset | Acute or subacute | Insidious |
| Course | Fluctuating | Progressive |
| Mental state | | |
| Arousal | Fluctuating | Normal |
| Language | Anomia | Aphasia |
| Speech | Slurred | Normal |
| Memory | Inattentive and forgetful | Amnesia |
| Hallucinations | Common | Less common |
| Motor system | Tremor, asterixis | Normal until late |
| Electroencephalogram | Diffusely slow | Normal early, mildly slow late |
| Computed tomographic scan | Normal or shows atrophy | Normal or shows atrophy |

icating variety due to intraventricular blockage by a mass lesion or chronic infection or the communicating variety (normal-pressure hydrocephalus) that may follow trauma, infection or subarachnoid hemorrhage.[8] The ventricular dilatation is associated with a triad of clinical signs including dementia, incontinence and gait disturbance. Although ventricular shunting does not reverse all cases, most patients with abnormal cisternograms and a compatible clinical syndrome have improvement following the surgical procedure.

Subdural hematomas, especially when bilateral, cause dementia that may be reversible with surgical drainage. Headaches, psychomotor slowing and a fluctuating course are more characteristic than focal signs. Subacute and chronic hematomas are revealed by brain imaging studies.

Infections such as chronic meningitis (tuberculous, fungal or parasitic), cerebral abscesses, granulomas and Whipple's disease are also among the intracranial disorders that may cause reversible dementia. In some cases these may be complicated by the development of a secondary obstructive hydrocephalus that requires separate treatment.

A number of inflammatory conditions such as systemic lupus erythematosus, giant cell arteritis, sarcoidosis and Behçet's syndrome affect intracerebral structures. These disorders may cause cerebral ischemia in addition to inflammation to produce dementia. Steroid therapy may help ameliorate the intellectual deficits in these conditions.[9,10]

### *Toxic, Metabolic and Systemic Disturbances*

Toxic and metabolic disorders frequently present as acute confusional states, and if the cause is not identified and corrected immediately, a chronic state ensues that must be differentiated from other causes of dementia. The clinical manifestations of toxic and metabolic disorders may vary with the underlying condition, but they often share common features that allow them to be distinguished from degenerative dementias such as Alzheimer's disease. Table 2 lists the features that may help differentiate between the two types of dementia. Systemic, toxic and metabolic disorders are more likely to have an acute or a subacute onset and to show a fluctuating course with exacerbations and remissions. Patients may exhibit decreased or increased arousal and variable attention to external stimuli. Although difficulty with naming is common, other aphasic symptoms are rare in chronic confusional states but common in Alzheimer's disease. Memory difficulties are prominent in both. Slurred speech, tremor and asterixis are motoric features of toxic-metabolic encephalopathies, whereas in Alzheimer's disease the motor system is normal until late in the clinical course. An electroencephalogram usually shows more pronounced slowing early in the course of a toxic-metabolic encephalopathy in comparison to that seen in Alzheimer's disease.

A wide variety of systemic and metabolic disorders can produce reversible dementia syndromes. The elderly suffer disproportionately from systemic illnesses and, because of a reduced capacity for homeostasis, are most vulnerable to the metabolic dementias. About 86% of persons older than 65 years have one chronic illness and 50% have two or more chronic medical conditions.[11] Changes in mental function may be the initial manifestation of systemic and metabolic illness in the elderly.[12] Table 1 lists the principal systemic causes of dementia, including cardiac and pulmonary disease, anemia, uremia, hepatic encephalopathy, electrolyte disturbances, endocrinopathies, vitamin deficiencies, systemic infections and inflammatory diseases. In most cases, treatment of the underlying condition restores mental function except when conditions such as vitamin $B_{12}$ deficiency or pronounced hypoxia produce structural neurologic damage that persists following treatment and leads to a more chronic dementia syndrome.

Toxic causes of dementia include heavy metal encephalopathies, organic solvent and pesticide exposure and a large number of over-the-counter and prescription medications (Table 1). The high frequency of medical illnesses in the elderly results in the use of multiple medications and a high potential for iatrogenic dementia.[13] Those older than 65 years, representing 11% of the US population, receive 30% of all prescribed medications. A similar disproportionate use occurs with over-the-counter medications: 70% of the elderly, compared with only 10% of young patients, regularly uses proprietary drugs.[14] Drug metabolism is altered in the elderly because of changes in the ratio of body fat to lean mass, decreased blood flow to detoxifying organs and changes in the absorption and serum protein binding of drugs. These alterations render the elderly more vulnerable to drug interactions and to the accumulation of toxic concentrations at doses recommended for younger patients. In addition, with advanced age, the brain may be more sensitive to the effects of many drugs even if routine dosages are administered.

These changes make it prudent to be conservative when prescribing medicines for the elderly. This includes eliminating unnecessary drugs, discouraging the excessive use of over-the-counter agents and using pharmacokinetic principles and serum drug assays whenever possible to avoid toxicity. It is always important to consider a prescribed drug as a poten-

tially reversible cause of dementia. In most patients, decreasing or eliminating exposure to the offending agent is sufficient to reverse the dementia syndrome. An interval of several weeks may be required between the identification and treatment of a toxic-metabolic disorder and the resolution of symptoms of intellectual decline.[15]

*Depression*

A final highly reversible type of dementia is that due to psychiatric disease, especially depression.[16,17] This is sometimes referred to as pseudodementia. These patients meet the criteria for dementia given above, however, and there is nothing false about their impairments in intellectual function. The course of dementia due to an affective disorder tends to be short, and there will often have been a prior episode of depression. Psychomotor slowing and changes in neurovegetative function may suggest a depression even when a patient does not admit to a sad mood. The patient performs poorly on psychometric tests and gives frequent "I don't know" responses. A depressed patient tends to be aware of his or her

TABLE 3.—*Treatable Dementias*

| *Disorder* | *Clinical Characteristics* | *Treatment* |
|---|---|---|
| Malignant gliomas; metastases | Headache; nausea; papilledema; seizures; progressive focal signs | Surgical decompression; steroids; irradiation |
| Multi-infarct dementia | Abrupt onset; fluctuating course; focal signs and symptoms; cardiovascular risk factors | Control hypertension, other risk factors; antiplatelet therapy; anticoagulation |
| Angular gyrus syndrome | Gerstmann's syndrome plus anomia, alexia; nonverbal memory and daily activities preserved | Treat underlying stroke or tumor |
| Post-trauma dementia | Closed head injury; memory loss; personality changes; focal signs; postconcussion syndrome | Rehabilitation program |
| Dementia pugilistica | Repeated blows to head; psychomotor slowing; extrapyramidal signs | Antiparkinsonian drugs |
| Neurosyphilis | General paresis; frontal lobe personality; 20 years after primary infection; positive serology, positive CSF; meningovascular lues, gummas, tabes dorsalis | High-dose intravenous administration of penicillin |
| Coccidioidomycosis | Pulmonary disease; Southwest US; erythema nodosum; basilar meningitis | Prolonged amphotericin B (intravenous or intrathecal); shunt hydrocephalus |
| Other fungal disease | Histoplasmosis; *Candida; Aspergillus;* mucormycosis; blastomycosis | Amphotericin B; flucytosine; ketaconazole |
| Amebiasis | Fulminant meningoencephalitis | Amphotericin B; rifampin; miconazole |
| Cysticercosis | *Tinea soleum;* basilar meningitis; parenchymal calcified cysts; seizures; hydrocephalus | Praziquantel; steroids; anticonvulsants |
| Progressive multifocal leukoencephalopathy | Immunocompromised host; focal signs; headache; multiple white matter lesions; papovavirus | Cytarabine; treat underlying disorder |
| Herpes encephalitis | Headache; fever; psychosis; seizures; hemorrhagic temporal lesions; EEG has focal repetitive spikes; residual amnesia | Vidarabine |
| Acquired immunodeficiency syndrome | Opportunistic infections of the CNS and systemically; encephalitis; T-cell abnormalities; lymphadenopathy | Treat infections |
| Multiple sclerosis | Fluctuating course; multiple lesions affecting vision, spine, bladder function; mood changes; memory loss | Steroids; immunosuppression |
| Epilepsy | Postictal confusion; myoclonic epilepsy; brain damage | Control seizures with optimal anticonvulsants |
| Parkinson's disease | Tremor; rigidity; bradykinesia | Levodopa-carbidopa combination; anticholinergics; amantadine HCl; bromocriptine mesylate |
| Huntington's disease | Familial chorea; psychiatric symptoms | Haloperidol for chorea and psychosis; antidepressants |
| Progressive supranuclear palsy | Decreased voluntary gaze, especially vertical; axial rigidity; gait difficulty | Antiparkinsonian drugs |
| Wilson's disease | Familial; dysarthria, dystonia, tremor; liver disease; Kayser-Fleischer rings; low serum ceruloplasmin; high urinary copper excretion | Penicillamine; low copper diet |
| Basal ganglia calcification | Parkinsonism or chorea; may be familial or associated with hypoparathyroidism | Treat endocrine disorder and movement disorder |
| Post-cardiac arrest anoxic encephalopathy | Acute cerebral hypoxia, carbon monoxide poisoning; myoclonus; seizures; spasticity; amnesia residual | Seizure control |
| Dialysis dementia | Dysarthria; agitation; myoclonus; EEG: slow wave bursts; aluminum toxicity | Diazepam |
| Acquired hepatocerebral degeneration | Chronic hepatic encephalopathy; dysarthria; ataxia; asterixis; choreoathetosis | Reduce dietary protein; lactulose; neomycin |
| Behçet's syndrome | Uveitis; oral and genital ulcers; aseptic meningitis with cranial nerve palsies | Steroids; immunosuppression |
| Cancer complications | Metastases; endocrine and metabolic effects; infections | Treat underlying malignancy and medical complications |
| Alcoholic dementia | Prolonged excess alcohol use; memory, abstraction poor; CT atrophy; distinguish from acute intoxication, withdrawal syndromes and Korsakoff's syndrome | Abstinence from alcohol |
| Mercury | Sensory changes; visual loss; dysarthria; tremors; psychosis | Penicillamine; eliminate exposure |
| Manganese | Neuropsychiatric and extrapyramidal symptoms | Edetate chelation |
| MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) | Synthetic heroin contaminant; parkinsonian syndrome | Antiparkinsonian drugs |
| Schizophrenia | Psychosis; fluctuating course | Neuroleptic agents |

CNS=central nervous system. CT=computed tomography. EEG=electroencephalogram

decreased intellectual capacity, and the findings of a neurologic examination and diagnostic evaluations are normal. At times an empiric trial of antidepressants is necessary to establish or to exclude the diagnosis. Depression due to other dementing conditions, such as systemic illnesses, intoxications or hydrocephalus, is a complication that may reverse with treatment of the underlying disorder.

## Treatable Dementias

Conditions causing permanent changes of the nervous system cannot be reversed with current medical techniques. Nevertheless, some of these conditions may be considered treatable because appropriate interventions will either alter the course of the dementia or relieve important related symptoms. Most, but not all, of these disorders are primary neurologic illnesses (Table 3).

One of the major causes of treatable dementia is cerebrovascular disease. Multi-infarct dementia may result from several clinically evident strokes or from many small lacunar infarcts in the basal ganglia and deep white matter of the brain. Hypertension, cardiovascular disease, diabetes mellitus, oral contraceptive use, arteritis and familial hyperlipidosis may predispose to strokes and hence to multi-infarct dementia. The Hachinski Ischemia Scale highlights the history, risk factors and focal features usually present in multi-infarct dementia.[18] Treatment is aimed at preventing ischemic events through the use of antiplatelet medications, the selective use of anticoagulants and carotid endarterectomy and reducing risk factors such as hypertension. With prophylaxis against repeat strokes and the natural neurologic recovery processes, there may be significant improvement in the cognitive and the physical difficulties associated with multiple infarcts.

The angular gyrus syndrome, usually caused by an infarct in the dominant parietal lobe, produces a multitude of intellectual deficits and may be confused with a degenerative dementia. The angular gyrus syndrome includes Gerstmann's tetrad—agraphia, acalculia, finger agnosia and right-left disorientation—alexia and anomia. Nonverbal memory, however, will be preserved, an important point distinguishing the condition from Alzheimer's disease.[19]

Posttraumatic dementia is a common cause of intellectual disability,[20] particularly in young people. It tends to be associated with prominent amnesia, focal neurologic signs and personality changes. The clinical features reflect the frontal and temporal preponderance of neuropathologic lesions resulting from closed head trauma. Comprehensive rehabilitation programs are necessary to maximize function. Anticonvulsant medications are used when the trauma is complicated by seizures. Associated neuropsychiatric disorders such as depression or psychosis may be treated with appropriate medications. Dementia pugilistica, a condition resulting from repeated blows to the head in boxers, manifests by psychomotor slowing and extrapyramidal signs such as rigidity, stooped posture and tremor. Antiparkinsonian medications may be helpful for these symptoms.

Most of the diseases of the extrapyramidal system are associated with cognitive and emotional difficulties.[3] Parkinson's disease, Huntington's disease, progressive supranuclear palsy, Wilson's disease and basal ganglia calcification all have distinctive clinical features with movement disorders and distinctive neuropathologic features. In Parkinson's disease, the use of dopaminergic compounds lessens the motor symptoms and may also enhance cognitive function.[21] This treatment is less effective in patients with progressive supranuclear palsy. Wilson's disease may be halted (or reversed if the pathology is not severe) by a regimen of penicillamine and a low copper diet. Basal ganglia calcification may be associated with an underlying endocrinologic disorder, hypoparathyroidism, which can be treated. Although the cognitive decline in Huntington's disease is inexorable, the chorea is reduced by the use of neuroleptic agents. Depression is a frequent accompaniment of Huntington's disease and Parkinson's disease, and treatment of the depression may lead to cognitive improvement. Medications used to treat extrapyramidal syndromes may lead to chronic confusional states, and, therefore, therapeutic interventions need constant monitoring.

Demyelination of subcortical white matter is frequently found in multiple sclerosis, and memory problems and other features of a mild dementia are common.[22] Exacerbations of multiple sclerosis are often associated with a worsening of cognitive function, and steroids or immunosuppressive therapy may be of benefit in altering the progression of symptoms.

Dementia associated with epilepsy may result from anticonvulsant toxicity, underlying brain lesions, frequent seizures or postictal confusion. Subtypes of myoclonic epilepsy cause progressive dementia, and in these cases control of seizures will partially limit cognitive impairment.

Although many infectious causes of dementia are reversible, some infections may produce permanent parenchymal brain damage and chronic dementia even when appropriately treated. For example, *Treponema pallidum* is sensitive to penicillin, but the damage caused in neurosyphilis is more often halted than reversed.[23] Likewise, treatment of fungal meningitis is extremely difficult, often requiring intrathecal administration of amphotericin B and ventricular shunting to relieve hydrocephalus; however, treatment can alter the otherwise fatal progression of these illnesses.

Viral causes of dementia are responsive to treatment. Herpes encephalitis is now managed with vidarabine therapy. Progressive multifocal leukoencephalopathy, a viral condition seen in conjunction with immunosuppression, may respond to treatment or may remit spontaneously.[24] In the current epidemic of the acquired immunodeficiency syndrome (AIDS), caused by the human immunodeficiency virus (HIV), opportunistic infections affect the brain.[25] AIDS is also frequently associated with an encephalopathy that may be a viral encephalitis.[26]

Various systemic illnesses may secondarily produce permanent neurologic damage. This is true of post-cardiac arrest anoxic encephalopathy. Control of seizures and supportive care are necessary. Chronic hepatic encephalopathy may lead to acquired hepatocerebral degeneration with dementia, dysarthria, ataxia, asterixis and choreoathetosis.[27] Treatment of this condition is similar to that of reversible hepatic encephalopathy, with the goal of halting the progression of the illness. Dialysis dementia results from excess aluminum in hemodialysis. The dysarthria, myoclonus, agitation and dementia may respond transiently to the administration of diazepam.[28]

Most toxic conditions are reversible. Dementia due to excessive alcohol abuse, however, is reversible only when the intake is of relatively short duration. In other cases, the dementia is stabilized by abstinence.[29] MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine), a potent neurotoxic by-

product of synthetic morphine, causes an irreversible syndrome similar to Parkinson's disease. The use of antiparkinsonian medications is helpful.[30]

Schizophrenia, a psychiatric disorder first described as dementia praecox, must be considered as a treatable dementia when intellectual impairment accompanies an acute psychotic episode.[4] The psychiatric history, the fluctuating course and the response to neuroleptics clarify the nature of the illness. Chronic schizophrenia is sometimes associated with progressive intellectual deterioration late in the course of the disease.

Reversible dementias may sometimes respond only partially to therapy, thus fitting into the treatable category. When this occurs, it may be that the condition persisted to the point of permanent brain damage or that the reserve capacity of an aging nervous system was overwhelmed.

## Treatable Aspects of Irreversible Dementias

Even in the case of a progressive, irreversible cause of dementia, there are treatable aspects that may improve a patient's level of function and quality of life.[31] The presence of a degenerative condition, such as Alzheimer's disease, does not confer immunity against the reversible and treatable conditions listed in Tables 1 and 3, and appropriate evaluations for these illnesses should be conducted when indicated.

General health maintenance may prevent medical complications of chronic disability. Medications, especially sedatives used to control the behavior of demented patients, may exaggerate symptoms of confusion and memory impairment. Monitoring medication dosages is essential and may require an aide or family member to supervise the patient. Similarly, it is important to ensure good nutrition. This is particularly true for elderly patients with mild dementia who may be living alone and eating improperly prepared meals and convenience foods with inadequate nutritional value.

Incontinence is frequently the problem that leads to placement of a patient in a nursing facility. Incontinence may result from focal neurologic damage, a side effect of medication, infection or other physical problem. When the incontinence is the result of cognitive impairment, a schedule of frequent toileting in the day and the use of incontinence pads at night may keep the patient clean and dry.

Patients with dementia do not adjust well to novelty; surroundings and schedules should be as consistent as possible. Regular caretakers with whom a patient is familiar are preferable to a constantly changing parade of newcomers. Moves to new homes should be done infrequently, and, if possible, the patient should keep as many personal effects as is practical to enhance the familiarity of the environment. Residences must be kept safe, with locks on cabinets containing dangerous items and medications, locks on doors leading outside and enough nighttime illumination to keep a nocturnal pacer from injury. Ideally the environment will also be stimulating with activities and companions geared to the age and cognitive capacity of a person.

Agitation, violence, hallucinations and delusions that lead to dangerous actions may require treatment. Low doses of major tranquilizers can effectively control these symptoms, with a choice of agents having relatively low sedation (haloperidol) or high sedation (chlorpromazine, thioridazine), as indicated. Short-acting benzodiazepines may help patients who have intermittent anxiety or mild agitation, with constant monitoring for the occurrence of side effects or behavioral worsening. Mild antihistaminic sedatives, low doses of major tranquilizers or short-acting hypnotics are helpful for problematic nocturnal wandering. The use of anticholinergic agents should be avoided. Medications should be used only to control serious behavior problems and not for the convenience of caretakers.

It is the role of a caretaker that ultimately determines the success or failure of all dementia treatment, and the needs of caretakers cannot be ignored. Caring for a patient with dementia creates an emotional, social and financial burden on the spouse or children. Adult day care and respite admissions to hospital may give a caretaker a break from the "36-hour day,"[32] allowing him or her to continue the care for a longer time. Social services, psychological support, financial assistance and legal counsel are often required in addition to medical advice. These needs will change with the stage of dementia.

## Evaluating Patients for Treatable Dementia

The number of potential causes for a patient's symptoms of intellectual decline is quite large,[4] and it is undesirable to rely on a series of laboratory tests to exclude systematically each of the possible conditions. Such an approach would be inefficient, expensive and invasive. Clinicians must develop a strategy to guide their selection of tests to arrive most expeditiously at an accurate diagnosis in each case. The primary goal is to identify treatable conditions contributing to the cognitive impairment. Very often the major obstacle to an accurate assessment is the attitude that intellectual decline is normal in the elderly or that all dementia is the result of Alzheimer's disease.

The initial history and general physical examination provide clues to the presence of toxic or systemic illnesses. A detailed neurologic examination alerts a clinician to the presence of localizing signs indicative of focal brain disease or to the existence of an extrapyramidal disorder. Tables 1 and 3 indicate the salient historical, physical and neurologic characteristics associated with various dementia-producing conditions. The presence of one or more of these features would lead a physician to include the relevant specific diagnostic investigations in the assessment.

A properly carried out mental state examination probes each domain of intellectual function as well as the emotional state of a patient. This adds invaluable diagnostic information. For example, in Table 2 the features consistent with a toxic or metabolic confusional state are contrasted with those of dementia of the Alzheimer type. Attention to specific features of a mental state examination can also aid in distinguishing Alzheimer's disease from the angular gyrus syndrome,[19] from the dementia associated with depression[17] and from the dementia syndromes of hydrocephalus and extrapyramidal syndromes.[4]

Certain laboratory investigations should be done routinely in evaluating all dementia patients. Tests that efficiently screen for the common medical illnesses of the elderly and those capable of detecting the most frequent dementias should be done in every case.[5] Complete blood counts, erythrocyte sedimentation rate, serum chemistry analysis, urinalysis, thyroid function tests, syphilis serology, serum $B_{12}$ level, electrocardiogram and a chest x-ray film constitute an initial medical evaluation. In addition, all patients with dementia should be scanned with either computed tomography or magnetic resonance imaging. Imaging the brain allows the detection of

occult tumors, chronic subdural hematomas, hydrocephalus and ischemic lesions. These conditions may be treatable if not reversible, and identifying or excluding them is of great value in establishing diagnostic certainty and in advising patients and families about prognosis. Similarly, an electroencephalogram should be done whenever possible. A normal study is expected in a patient with early Alzheimer's disease and in one with dementia due to depression. Diffuse slowing is indicative of a toxic or metabolic condition, while focal slowing reflects localized structural pathology.[33] Cerebrospinal fluid analysis is important whenever an infectious or inflammatory process is suspected.

Treatable and reversible conditions can be superimposed on degenerative diseases, and the routine workup outlined above should be done even when the presumptive diagnosis is Alzheimer's disease or some other progressive dementia. Specialized or invasive tests are done when there is a specific indication based on the initial evaluation. Two clinical situations routinely requiring more extensive investigation are dementia in a young person and dementia with uncommon or atypical features.

## Conclusion

Dementia is a clinical syndrome of acquired persistent intellectual impairment produced by brain dysfunction. The disorders causing dementia entail a spectrum of treatability: in some cases, timely intervention will cure the underlying condition and restore intellectual function; in others, treatment will halt further deterioration or modify important symptoms without reversing the cognitive losses; in still others, appropriate management cannot reverse or halt the disease process, but therapy will maximize remaining abilities and prevent unnecessary complications. Attention to the treatable aspects of all dementing disorders will increase detection of reversible conditions, decrease the burden on a patient's family, enhance the quality of a patient's life and prevent premature nursing home placement.

### REFERENCES


1. Cummings J, Benson DF, LoVerme S: Reversible dementia: Illustrative cases and review. JAMA 1980; 243:2434-2439

2. Plum F: Dementia: An approaching epidemic. Nature 1979; 279:372-373

3. Beck JC, Benson DF, Scheibel AB, et al: Dementia in the elderly: The silent epidemic. Ann Intern Med 1982; 97:231-241

4. Cummings JL, Benson DF: Dementia: A Clinical Approach. Boston, Butterworths, 1983

5. Larson EB, Reifler BV, Featherstone HJ, et al: Dementia in elderly outpatients: A prospective study. Ann Intern Med 1984; 100:417-423

6. McKhann G, Drachman D, Folstein M, et al: Clinical diagnosis of Alzheimer's disease. Neurology (NY) 1984; 34:939-944

7. Cummings JL, Benson DF: Dementia of the Alzheimer type. J Am Geriatr Soc 1986; 34:12-19

8. Benson DF: Hydrocephalic dementia, *In* Vinken PJ, Bruyn GW, Klawans HL (Eds): Handbook of Clinical Neurology, revised series—Vol 2(46), Fredericks JAM (Ed): Neurobehavioural Disorders. Amsterdam, Elsevier, 1985

9. Moore PM, Cupps TR: Neurological complications of vasculitis. Ann Neurol 1983; 14:155-167

10. Bengtsson BA, Malmvall BE: Giant cell arteritis. Acta Med Scand [suppl] 1982; 658:1-102

11. Jarvik LF, Perl M: Overview of physiologic dysfunctions related to psychiatric problems in the elderly, *In* Levenson AJ, Hall RCW (Eds): Neuropsychiatric Manifestations of Physical Disease in the Elderly. New York, Raven Press, 1981

12. Lipowski ZJ: Transient cognitive disorders (delirium, acute confusional states) in the elderly. Am J Psychiatry 1983; 140:1426-1436

13. Ouslander JG: Drug therapy in the elderly. Ann Intern Med 1981; 95:711-722

14. Thompson TL, Moron MG, Nies AS: Psychotropic drug use in the elderly. N Engl J Med 1983; 308:134-138, 194-199

15. Blass JP, Plum F: Metabolic encephalopathies in older adults, *In* Katzman R, Terry R (Eds): The Neurology of Aging. Philadelphia, FA Davis, 1983

16. Wells CE: Pseudodementia. Am J Psychiatry 1979; 136:895-900

17. Caine ED: Pseudodementia. Arch Gen Psychiatry 1981; 38:1359-1364

18. Hachinski VC, Iliff LD, Zilhka E, et al: Cerebral blood flow in dementia. Arch Neurol 1975; 32:632-637

19. Benson DF, Cummings JL, Tsai SY: Angular gyrus syndrome simulating Alzheimer's disease. Arch Neurol 1982; 39:616-620

20. Levin HS, Benton AL, Grossman RG: Neurobehavioral Consequences of Closed Head Injury. New York, Oxford University Press, 1982

21. Halgin R, Riklan M, Misiak H: Levodopa, parkinsonism, and recent memory. J Nerv Ment Dis 1977; 164:268-272

22. Peyser JM, Edwards KR, Poser CM, et al: Cognitive function in patients with multiple sclerosis. Arch Neurol 1980; 37:577-579

23. Hotson JR: Modern neurosyphilis: A partially treated chronic meningitis. West J Med 1981; 135:191-200

24. Price RW, Nielsen S, Horten B, et al: Progressive multifocal leukoencephalopathy: A burnt-out case. Ann Neurol 1983; 13:485-490

25. Snider WD, Simpson DM, Nielsen S, et al: Neurological complications of acquired immune deficiency syndrome: An analysis of 50 patients. Ann Neurol 1983; 14:403-418

26. Shaw GM, Harper ME, Hahn BH, et al: HTLV-III infection in brains of children and adults with AIDS encephalopathy. Science 1985; 277:177-181

27. Victor M, Adams RD, Cole M: The acquired (non-Wilsonian) type of chronic hepatocerebral degeneration. Medicine (Baltimore) 1965; 44:345-396

28. Nadel AM, Wilson WP: Dialysis encephalopathy: A possible seizure disorder. Neurology (Minneap) 1976; 26:1130-1134

29. Cutting J: Alcoholic dementia, *In* Benson DF, Blumer D (Eds): Psychiatric Aspects of Neurologic Disease, Vol 2. New York, Grune & Stratton, 1982

30. Ballard PA, Tetrud JW, Langston JW: Permanent human parkinsonism due to 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)—Seven cases. Neurology 1985; 35:949-956

31. Rabins PV: Management of irreversible dementia. Psychosomatics 1981; 7:591-597

32. Mace N, Rabins P: 36-Hour Day. Baltimore, Johns Hopkins University Press, 1981

33. Harner RN: EEG evaluation of the patient with dementia, *In* Benson DF, Blumer D (Eds): Psychiatric Aspects of Neurologic Disease. New York, Grune & Stratton, 1975

# Cardiac Ischemia. Part I—Metabolic and Physiologic Responses

*Moderator*
GLENN A. LANGER, MD
*Discussants*
JAMES N. WEISS, MD, *and* HEINRICH R. SCHELBERT, PhD

*An edited summary of an Interdepartmental Conference arranged by the Department of Medicine of the UCLA School of Medicine, Los Angeles. The Director of Conferences is William M. Pardridge, MD, Professor of Medicine.*

*In the ischemic state, which leads to myocardial infarction, there is a gradation of cardiac muscle injury and a sequence of functional loss. On coronary occlusion an immediate cellular leak of potassium occurs and the rate of relaxation declines. Within 1 to 2 minutes there is complete loss of contraction followed by the onset of contracture in 7 to 10 minutes in isolated preparations. The major problem of this initial period, if the occlusion zone is not too great, is electrical dysfunction. The next 1 to 6 hours is the period of variable reversible injury. Positron emission tomography technique and fatty acid and carbohydrate tracers quantitatively assess regions that are metabolically competent. The problem is to maintain and improve the competence of these regions during reperfusion, whether by thrombolytic therapy (streptokinase) or tissue plasminogen activator, percutaneous transluminal angioplasty, acute coronary artery bypass graft or by total vented bypass and regional reperfusion without thoracotomy (procedure under development).*

(Langer GA, Weiss JN, Schelbert HR: Cardiac ischemia. Part I—Metabolic and physiologic responses. [Specialty Conference]. West J Med 1987 Jun; 146:713-723)

GLENN A. LANGER, MD:* Although major advances in our understanding and treatment of ischemic heart disease have occurred during the past 20 years, half a million Americans still die of this disease each year.[1] Further advances in treatment will depend on new knowledge of the atherosclerotic process in coronary arteries, the response of the myocardium to deprivation of its blood supply and its response to various types of reperfusion. In this conference we shall focus on the last two of these and, in addition, review current and future therapy.

## Cardiac Metabolism

The heart under normal conditions is dependent on aerobic metabolism for more than 90% of its requirements. Glycolysis, when adequate oxygenation is present, contributes less than 10% to total adenosine triphosphate (ATP) production.[2] At basal levels of function, fatty acid is the preferred substrate (60% or greater) with the remainder being supplied largely by carbohydrate. The aerobic path is the most efficient for the conversion of substrate into ATP. A molecule of glucose metabolized through the citric acid cycle yields 34 mol of ATP; a molecule metabolized glycolytically yields 2 mol of ATP. If the aerobic pathway is shut down, as in ischemia or hypoxia, the pyruvate formed from glycolysis is reduced to lactate with accompanying oxidation of nicotinamide adenine dinucleotide (NADH → NAD).

*Professor of Medicine and Physiology, Director of Cardiovascular Research, UCLA School of Medicine.

Oxygen is delivered to the myocardium via the coronary vessels. The heart is unique in the amount of oxygen it extracts from the coronary capillary blood; under basal conditions it is 75%, which is nearly maximal (as compared with the 20% to 25% extraction by most of the rest of the body). Therefore, an increased oxygen demand by the heart muscle must be met by a proportional increase in coronary flow. With a normally responsive coronary vasculature, coronary flow is responsive to metabolic requirement through a sensitive feedback system.[3] The increased use of ATP, or deficient production, causes increased levels of adenosine diphosphate (ADP) and adenosine monophosphate (AMP). The latter is dephosphorylated to adenosine at the myocardial cell margin by 5′-nucleotidase. Adenosine is an extremely potent vasodilator and its presence in the intestinal fluid causes arteriolar dilation. This increases coronary flow, which provides more substrate and oxygen and enables increased phosphorylation and replenishment of ATP.

Ventricular oxygen consumption at rest is about 9 ml per 100 grams per minute.[4] This oxygen is distributed according to the requirements of the systems responsible for the various cellular functions. About 20% of the metabolism of a heart beating at a rate of 80 beats per minute is directed toward maintaining a basic metabolic state—that is, keeping the cell alive in the absence of any electrical or mechanical activity. Protein synthesis and replacement of structural components are in this category. Less than 5% of oxygen is consumed in

Part I of a two-part conference. Part II to be published in a subsequent issue.

This study was supported in part by National Institutes of Health grants RO1 HL28539 (Dr Langer), 1R 23 HL27846 (Dr Weiss), HL29845, HL33177 (Dr Schelbert), HL16292 (Dr Buckberg); United States Department of Energy grant DE-AC03-76-SF00012 (Dr Schelbert); Investigative Group Award (Dr Schelbert); Grant-in-Aid from the American Heart Association, Greater Los Angeles Affiliate, and the Laubisch Endowment (Dr Weiss).

Reprint requests to Glenn A. Langer, MD, Department of Medicine and Physiology, Cardiovascular Research Laboratory, A3-375 Center for Health Sciences, UCLA School of Medicine, Los Angeles, CA 90024.

ABBREVIATIONS USED IN TEXT

ADP = adenosine diphosphate
AMP = adenosine monophosphate
ATP = adenosine triphosphate
$[Ca^{++}]$ = calcium ion concentration
CoA = coenzyme A
$CoQ_{10}$ = coenzyme $Q_{10}$
FDG = fluoro-2-deoxyglucose
IV = intravenous
$[K^+]_o$ = extracellular potassium ion concentration
PET = positron emission tomography
PTCA = percutaneous transluminal coronary angioplasty
TPA = tissue plasminogen activator
TTC = triphenyltetrazolium chloride
$V_{max}$ = action-potential upstroke velocity

support of electrical activity. This metabolism is to maintain the steady-state levels of sodium and potassium within the cell. The maintenance of these ionic gradients is required for the generation of action potentials on changes in sarcolemmal membrane conductance. The energy is expanded in the operation of the sodium-potassium pump under control of sarcolemmal sodium-potassium adenosine triphosphatase. Another 15% of metabolism is required to pump calcium into the intracellular vesicular system—the sarcoplasmic reticulum. This system pumps two calcium ions for each ATP hydrolyzed, is under control of a sarcotubular calcium-adenosine triphosphatase and is responsible for decreasing intracellular calcium concentration to levels at which the muscle can relax. The remaining 60% of oxygen consumed is directed to the contractile process; two thirds (40%) of this oxygen is required to develop force within the cell ("internal tension"), which never appears as external work. These internal forces are applied to elastic and viscous structures in the cell. This leaves 20% of oxygen consumption to be applied to the accomplishment of the external work required to pump blood. With a component lost to heat, it is clear why the mechanical efficiency of the cardiac pump is less than 20%.

*Priority of Energy Dispensation*

With the onset of ischemia the functions described above do not fail with the same time course nor do they fail in an order predicted by the proportion of energy they consume. Within seconds of the onset of severe ischemia two events occur: first, the rate of relaxation slows 60 to 90 seconds before the rate of contraction begins to decline.[5] This is long before a significant decline in cellular ATP occurs and, therefore, cannot be attributed to a direct effect on the myofilaments. The process of calcium sequestration is probably compromised rapidly by the decreased blood flow. The other immediate effect is a rapid rise in extracellular potassium.[6,7] This rise is not due to failure of the sodium-potassium pump (see below) but is attributable to a leak across the sarcolemma, possibly to altered conductance of an ATP-dependent potassium channel in the membrane (see Dr Weiss's discussion). This leak can increase extracellular potassium concentration by threefold to fourfold within ten minutes of the onset of ischemia.

In isolated preparations, active force then begins to decline and, with total ischemia, reaches zero within two to three minutes. Rest or diastolic tension does not begin to rise for seven to ten minutes, with full contracture development taking 20 minutes or more[8] in isolated preparations. This late contracture is probably better defined as rigor. When there is insufficient ATP at the myofilaments to permit actin to detach from myosin, rigor occurs; it begins when ATP during ischemia falls to about 50% normal level.[8]

The last system to fail is the sodium-potassium pump.[8,9] This system functions without evidence of failure for 20 to 25 minutes in a total anaerobic state. It, then, has the highest priority for whatever energy remains in the cell. Teleologically the preferential maintenance of this pump makes sense; its failure leads to electrical inexcitability. If the cell cannot be excited, it makes little difference if it can contract or relax.

## Ionic, Electrophysiologic and Contractile Responses to Ischemia

JAMES N. WEISS, MD:* The immediate effects of interruption of blood flow to the myocardium are profound. Within seconds active tension development declines and is completely abolished within five minutes, depending on the experimental model used. Electrophysiologic abnormalities that predispose the heart to often lethal arrhythmias, such as ventricular fibrillation, also begin to manifest themselves within seconds after the onset of ischemia, although they are not rapid enough to explain the contractile dysfunction. The electrical instability of the heart during acute ischemia remains the major cause of mortality from coronary artery disease today. Of the more than 1 million cases of myocardial infarction in the United States each year, about 40% of patients die before reaching a hospital, most succumbing to lethal arrhythmias.[10] Recently studies of the effects of acute coronary artery occlusion in humans during coronary angioplasty have confirmed the similarities between the human and animal responses to acute ischemia.[11] As ischemia progresses, electromechanical activity is progressively inhibited, and after a period ranging from 20 to 60 minutes, irreversible damage begins to occur.[12] Once this stage has been reached, reperfusion is associated with leakiness of the cell membrane resulting in enzyme loss (for example, creatine kinase) and a defect in the ability of cells to regulate intracellular $Ca^{++}$. The latter results in the development of maintained diastolic tension (contracture) upon reperfusion, manifested histologically by contraction band necrosis and clinically in the phenomenon of "stone heart," a not uncommon complication of open-heart surgical procedures before the use of effective cardioplegic regimens became standard practice.

The pathogenesis of cardiac dysfunction during acute ischemia has been investigated intensively. Ischemia, however, is a complex event; not only the impairment of metabolism but also the accumulation of toxic metabolic by-products due to the lack of washout contribute to cardiac dysfunction. Furthermore, some of the complications of ischemia, such as early arrhythmias, depend largely on the inhomogeneity of the cellular environment between ischemic and adjacent normal myocardium. Despite these complexities, much information about the relation between cardiac function and metabolism has been gained from experimental models ranging from coronary occlusion in in vivo animal hearts to studies of single cardiac cells in which various components of ischemia can be simulated although genuine ischemia cannot be created.

Some of the factors that contribute to the development of electrophysiologic abnormalities during acute ischemia are summarized in Table 1. These factors lead to cellular depolarization, decreased excitability, depression of the action-po-

*Associate Professor of Medicine, Division of Cardiology, UCLA School of Medicine.

tential upstroke velocity ($V_{max}$), shortening of the action-potential duration and altered refractoriness. They cause pronounced slowing of conduction and unidirectional conduction block within the ischemic zone, favoring the development of reentrant arrhythmias and accounting for the high incidence of ventricular fibrillation within the first 20 minutes of coronary occlusion.[13] Injury currents arising from the ischemic tissue may excite adjacent normal tissue, producing extrasystoles that serve as the trigger for reentry.[14] After this initial period, the frequency of arrhythmias decreases transiently for several hours, after which ventricular extrasystoles reappear as a result of enhanced automaticity in damaged subendocardial Purkinje fibers overlying the area of infarct.[15] Extracellular accumulation of potassium ion ($[K^+]_o$) plays a major role in contributing to the acute electrophysiologic alterations of ischemia.[16-18] Studies in vivo of pig and dog hearts have documented increases in $[K^+]_o$ of up to 12 mEq per liter in the central ischemic zone within ten minutes after coronary occlusion.[19-21] $[K^+]_o$ rises in a triphasic pattern characterized by an initial rapid increase leading to a plateau phase after about 10 minutes, followed by a secondary rise after about 25 minutes (Figure 1). The latter phase probably reflects a loss of sarcolemmal integrity and is associated with irreversible cellular damage on reperfusion.[6,20] Several mechanisms may contribute to the elevation of $[K^+]_o$ during acute ischemia, including an increase in sarcolemmal $K^+$ conductance, $K^+$ efflux linked to the efflux of intracellularly generated anions (such as lactate and inorganic phosphate) to maintain electroneutrality of transsarcolemmal charge movement and an increase in $[K^+]_o$ due to a loss of free water from the extracellular space as osmotically active metabolic byproducts are generated intracellularly. Reduced $K^+$ influx from suppression of the $Na^+$-$K^+$ pump does not seem to contribute to cellular $K^+$ loss until late (more than 30 minutes) in ischemia.[6,22,23] In single ventricular cells, metabolic inhibition causes a sharp increase in $K^+$ conductance, which, by increasing outward current during depolarization, greatly shortens the action-potential duration,[24] similar to that which occurs with ischemia (Figure 1). Shortening of the action-potential duration during ischemia is one of the prominent early electrophysiologic alterations and cannot be attributed to the elevation in $[K^+]_o$ alone.[18] Recently patch-clamp experiments have shown that the cardiac sarcolemma contains an ATP-sensitive $K^+$ channel that is activated when the internal ATP falls below a critical level and is responsible for the increased $K^+$ conductance during exposure to metabolic inhibitors.[25-27] The increase in $K^+$ conductance and degree of action-potential shortening during hypoxia in multicellular preparations are attenuated by supplying the myocardium with exogenous glucose[18,28]; glycolysis may be a preferential source of ATP for maintaining sarcolemmal function during hypoxia and ischemia.[28-32]

Other factors listed in Table 1 also contribute significantly to arrhythmogenesis during ischemia. Acidosis significantly exacerbates the electrophysiologic alterations produced by elevated $[K^+]_o$.[18] Lactate has electrophysiologic effects independent of its effects on pH.[33] Catecholamine release and its extracellular accumulation due to lack of washout are significant during ischemia and have important arrhythmogenic influences. By increasing intracellular cyclic-AMP levels, catecholamines augment the slow $Ca^{++}$ channel and facilitate slowly conducting action potentials and triggered and nontriggered automaticity in depressed myocardium. Activation of intracellular phospholipases during early ischemia results in the generation of lysophospholipids, such as lysophosphatidyl choline, which contribute to cyclic-AMP elevation and also have substantial electrophysiologic effects of their own.[34] These compounds cause a reduction in $K^+$ conductance leading to cellular depolarization[35] and can produce changes in excitability, $V_{max}$ and refractoriness resembling ischemia. Their effects are potentiated by acidosis. Derangements in fatty acid metabolism during ischemia lead to the intracellular accumulation of fatty acid esters, particularly long-chain acylcarnitines, which have been shown to cause electrophysiologic alterations mimicking ischemia. Fatty acid esters may interfere with the $Na^+$-$K^+$ pump and intracellular membrane-mediated function as well. Both lysophospholipids and fatty acid esters are thought to act in low concentrations by inserting into membranes and modifying their functions and in higher concentrations by a detergent-like effect. Whether they accumulate rapidly enough and in suffi-

TABLE 1.—*Factors Contributing to Electrophysiologic Abnormalities During Acute Ischemia*

| |
|---|
| Elevated extracellular potassium concentration |
| Intracellular acidosis |
| Lactate accumulation |
| Catecholamine release |
| Elevated intracellular cyclic adenosine monophosphate |
| Lysophospholipid accumulation |
| Fatty acid ester accumulation |
| Free fatty acid accumulation |
| Free radicals |

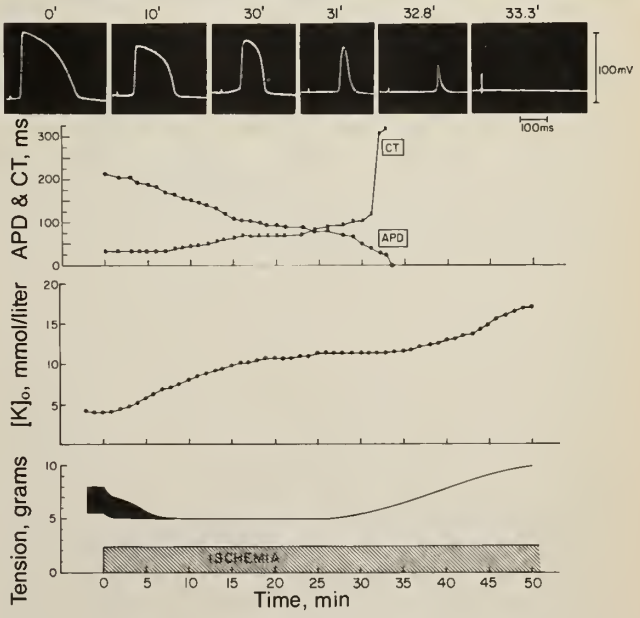



**Figure 1.**—Changes in the action-potential duration (APD), conduction time (CT), extracellular potassium concentration ($[K^+]_o$) and tension during a 50-minute period of global ischemia in an isolated rabbit interventricular septum are shown. The upper panel shows representative action potentials recorded at various times after the onset of ischemia, from which the action-potential duration and conduction time from the site of stimulation to recording site have been measured and plotted in the graph below. The third panel shows the change in $[K^+]_o$ measured with an intramyocardial $K^+$-sensitive electrode, showing the triphasic pattern of $[K^+]_o$ accumulation. The lower panel shows changes in the peak systolic and diastolic tension during the ischemic period. The development of contracture coincides with the secondary rise in $[K^+]_o$.

cient quantity to account for the earliest electrophysiologic changes during ischemia remains controversial, however. Elevated free fatty acid levels may also have direct arrhythmogenic effects in ischemic tissue.[34] Finally, the generation of free radicals during ischemia and reperfusion has recently received a great deal of attention as a possible mediator of membrane dysfunction.[36] Free radicals may produce pronounced electrophysiologic changes in isolated preparations,[37] and free radical scavengers reduce the incidence of reperfusion arrhythmias.[38] Their precise role in ischemic arrhythmogenesis is unestablished, however.

The cause of the immediate severe impairment of tension development during myocardial ischemia (Figure 1) remains controversial. Several hypotheses have been proposed: (1) collapse of the vascular architecture, which reduces myofibrillar stretch and shifts the heart to a lower position on the Starling curve; (2) the negative inotropic effect of intracellular acidosis: (3) reduction in intracellular free calcium concentration ($[Ca^{++}]$) resulting from the liberation of large amounts of inorganic phosphate (from high-energy phosphate breakdown) that exceeds the solubility product of calcium monohydrogen phosphate; (4) a decrease in transsarcolemmal $Ca^{++}$ influx, and (5) the ATP depletion at the myofilaments or at critical sites regulating intracellular free $[Ca^{++}]$, or both.

The first hypothesis cannot account for the similarity in the timing and severity of contractile dysfunction during ischemia to that during hypoxia, in which maintained flow prevents the vasculature from collapsing.[39] Direct measurement of intracellular pH during ischemia with nuclear magnetic resonance using phosphate 31 suggested that the rate of development of intracellular acidosis was not sufficiently rapid to account fully for the early decline in tension.[40] Also, during hypoxia without glucose present as substrate, the decline in tension was almost as rapid as during ischemia, yet the magnitude of acidosis was greatly attenuated due to washout.[39] The addition of glucose during hypoxia significantly exacerbated acidosis, but caused less severe impairment of tension development.[39] The third hypothesis seems plausible based on calculations of the expected increase in inorganic phosphate from high-energy phosphate breakdown during ischemia.[41] Furthermore, during combined inhibition of glycolytic and oxidative metabolism, intracellular free $[Ca^{++}]$ measured optically with $Ca^{++}$-sensitive dye aqueorin was shown to decrease rapidly in conjunction with the decline in contractile force.[42] During selective inhibition of oxidative metabolism, however, tension decline was not accompanied by a decrease in intracellular free $[Ca^{++}]$. The latter situation may be the more relevant to ischemia because glycolytic flux is increased during the initial minutes when the major decline in contractile force occurs. The fourth hypothesis has been rejected based on the finding that the influx of radioisotopically measured transmembrane $Ca^{++}$ did not decrease significantly during early hypoxia.[43] The final hypothesis that high-energy phosphate depletion is the cause of contractile dysfunction during ischemia is flawed by the observation in most studies that total cellular levels of high-energy phosphates did not fall rapidly enough to account for the decrease in active tension development. To make this hypothesis tenable, it has been proposed that the free energy of ATP hydrolysis may be more pertinent to maintaining contractile function than ATP levels per se.[44] The free energy change of ATP hydrolysis is given by the equation

$$\Delta G = \Delta G^{o} + RT\ln([ATP]/[ADP][P_i])$$

where $G$ = free energy, $G^{o}$ is the standard free energy at unit concentrations of ATP and ADP, $R$ = gas constant, $T$ = absolute temperature and $P_i$ = inorganic phosphate, and decreases rapidly during ischemia due to the accumulation of ADP and $P_i$. Alternatively, it has been postulated that a compartmentalized pool of high-energy phosphates preferentially used for force development is depleted more rapidly during ischemia than is reflected by total cellular high-energy phosphate levels.

Although this remains a highly controversial topic, considerable evidence supporting such compartmentation of metabolic energy in the heart has recently emerged. Based on the observation that creatine phosphate levels fall much more rapidly than ATP levels during ischemia despite the rapid kinetics of the creatine kinase reaction, Gudbjarnason and associates postulated that ATP becomes effectively trapped in mitochondria during ischemia, unable to be used in the cytoplasm by energy-consuming processes.[45] Recently nuclear magnetic resonance studies using $^{31}P$ have supported the existence of the creatine phosphate energy shuttle, in which creatine phosphate acts as the preferential cytoplasmic transport mechanism for supplying energy to the contractile apparatus.[46] According to this scheme, mitochondrial ATP reacts with mitrochondrial-bound creatine kinase to generate creatine phosphate, which diffuses through the cytoplasm to the myofilaments where it interacts with myosin-bound creatine kinase to regenerate ATP from ADP locally at the myofilament (Figure 2). Other evidence suggests that high-energy phosphates generated by mitochondrial metabolism are used preferentially for tension development, whereas glycolytically generated high-energy phosphates are used preferentially to support sarcolemmal function.[29-32,47] For example, during low-flow ischemia in the isolated Langendorff rat heart, concomitant inhibition of glycolysis resulted in much greater enzyme loss and contracture development on reperfusion than concomitant inhibition of oxidative metabolism despite identical total cellular levels of high-energy phosphates in the two cases.[29,47] In isolated arterially perfused rabbit septum,[32] selectively inhibiting oxidative metabolism caused a notable loss of developed tension, but only modest $[K^{+}]_o$ accumulation measured with intramyocardial $K^{+}$ sensitive electrodes. In contrast, selectively inhibiting glycolysis had little effect on developed tension but caused pronounced $[K^{+}]_o$ accumulation (Figure 3). The dosages of the metabolic inhibitors (iodoacetate, dinitrophenol and sodium azide) were adjusted so that total cellular levels of high-energy phosphates were not significantly different from control levels despite causing substantial abnormalities in cardiac function. The interpretation of these findings was that during selective partial inhibition of oxidative metabolism, glycolysis accelerated to maintain normal total cellular levels of high-energy phosphates, but the glycolytically generated high-energy phosphates could not be effectively used by the contractile apparatus to maintain normal tension. Conversely, during selective inhibition of glycolysis, oxidatively generated high-energy phosphates could not be effectively used by the sarcolemma to prevent cellular $K^{+}$ loss. Glycolytic enzymes bound to the sarcolemma may deliver high-energy phosphates into a relatively nondiffusible pool supplying sarcolemmal functions (Figure 2), consistent with the findings in other tissues.[48,49] If it exists in heart, compartmentation of metabolic energy is only partial because combined inhibition of glycolytic and oxidative metabolism had much more severe

effects on cellular $K^+$ loss and force development than selective inhibition of either pathway alone.[32]

Impairment of diastolic relaxation is one of the earliest manifestations of contractile dysfunction during ischemia and can be shown echocardiographically or angiographically in humans during angina.[50] This phenomenon has been attributed to a reduced ability of the sarcoplasmic reticulum of the myocardium to remove $Ca^{++}$ from the cytoplasm. As ischemia progresses, diastolic relaxation becomes incomplete and contracture develops (Figure 1), often heralding the onset of further contracture and irreversible damage on reperfusion. Ischemic contracture is best observed in isolated preparations made globally ischemic. During regional ischemia following coronary artery occlusion, the normal contraction of the nonischemic portions of the heart tends to passively distend the ischemic segment, causing paradoxic systolic bulging and masking the diastolic abnormalities. The cause of ischemic contracture is not definitively known, but has been attributed to either a defect in cellular $Ca^{++}$ homeostasis leading to an increased free $[Ca^{++}]$ in the vicinity of the myofilaments, or a rigor state induced by depletion of ATP. In the latter case, depletion of ATP at the myofilaments would prevent the crossbridge of the actin-myosin complex from releasing, resulting in maintained tension even when the cell was repolarized. Measurement of intracellular $[Ca^{++}]$ with $Ca^{++}$-sensitive microelectrodes during exposure to metabolic inhibitors has shown an increase in intracellular $[Ca^{++}]$ coinciding with the onset of contracture, but similar measurements using the $Ca^{++}$-sensitive dye aqueorin have produced opposite results.[51] If contracture in this setting is due to $Ca^{++}$ overload, it must be caused by malfunction of the intracellular organelles that buffer cytosolic-free $[Ca^{++}]$, such as the sarcoplasmic reticulum and mitochondria. An increased $Ca^{++}$ burden from extracellular sources is unlikely, because radioisotopically measured transsarcolemmal $Ca^{++}$ influx does not increase significantly during hypoxic contracture.[43] If, on the other hand, ischemic contracture is due to rigor from ATP depletion, it has been shown that the total cellular ATP level at which ischemic contracture develops is not fixed but varies depending on the type of metabolic substrate supplied to the heart.[52] Contracture developed at higher total cellular ATP levels during total ischemia in hearts preexposed to oxygenated perfusate containing acetate (mitochondrial substrate) than to hypoxic perfusate containing glucose (glycolytic substrate), suggesting that glycolytically generated ATP was more effective than oxidatively generated ATP at preventing contracture. Glucose is also effective in delaying the onset of contracture during hypoxia.[43] Perhaps a relevant point is that it has been shown that glycogenolytic enzyme complexes are bound to the sarcoplasmic reticulum in heart.[53] These findings again raise the issue of compartmentation of glycolytic versus oxidative metabolism in heart.

Based on the observations described above, apparently glycolysis has an important influence on cardiac function during ischemia. In particular, glycolytic metabolism supports sarcolemmal and possibly sarcoplasmic reticulum function during acute ischemia, although it is not capable of supplying all of the energy needs of the myocardium when oxidative metabolism is shut down. Ironically, Neely and Grotyohann have recently reported that the accumulation of glycolytic by-products during ischemia correlated inversely with the ultimate recovery of function on reperfusion.[54] Recovery bore no relation to total cellular levels of high-energy phosphates just before reperfusion. By supporting cardiac function during ischemia—that is, by failing to shut down energy-consuming processes—glycolysis could adversely affect ultimate recovery on reperfusion. These issues must be resolved in order that effective strategies may be developed to

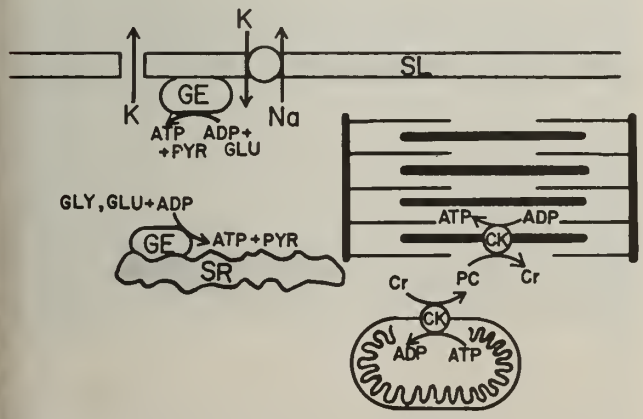



**Figure 2.**—The schema depicts the hypothetical basis for compartmentation of glycolytic and oxidative metabolism in heart. The creatine phosphate energy shuttle (see text) preferentially delivers energy to the contractile apparatus. Glycolytic enzymes (GE) bound to the sarcolemma (SL) preferentially supply adenosine triphosphate (ATP) to $K^+$ channels and possibly other sarcolemmal sites. Glycolytic enzymes bound to the sarcoplasmic reticulum (SR) may be an important source of energy for removal of $Ca^{++}$ from the cytoplasm. ADP = adenosine diphosphate, CK = creatine kinase (bound), Cr = creatine, GLU = glucose, GLY = glycogen, Na = sodium, PC = phosphocreatine, PYR = pyruvate

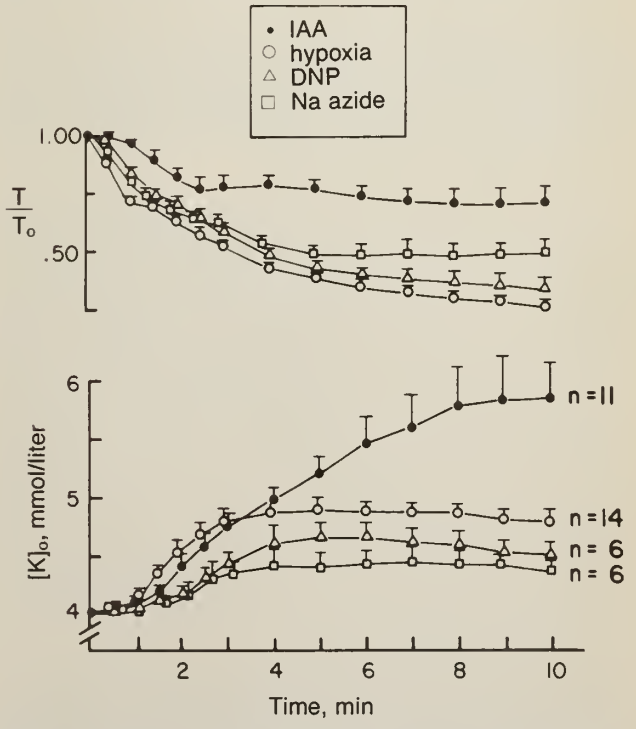



**Figure 3.**—The effects of selective inhibition of glycolytic versus oxidative metabolism on tension ($T/T_0$) are compared with those on extra-cellular potassium accumulation ($[K^+]_o$) in isolated arterially perfused rabbit interventricular septa. Glycolysis was inhibited by adding 1 mmol per liter iodoacetate (IAA) to glucose-free perfusate containing pyruvate as substrate for oxidative metabolism (●). Oxidative metabolism was inhibited with hypoxia (○), 0.01 mmol per liter dinitrophenol (DNP) (△) or 1 mmol per liter sodium azide (□) with glucose present as substrate for glycolysis. Values are mean ± standard error.

minimize the functional consequences of ischemia. That different metabolic pathways possibly are preferentially linked to specific cardiac functions may lead to a means of more effectively manipulating the outcome of ischemia.

## Metabolic Response to Ischemia

*Use of Positron Emission Tomography*

HEINRICH R. SCHELBERT, PhD:* Metabolic consequences of myocardial ischemia have been well characterized in in vitro experimental systems[55,56] and can now be approached and tested with positron emission tomography (PET).

The ability of PET to identify, noninvasively, regional alterations in substrate metabolism induced by ischemia was initially tested in animals. Acute myocardial ischemia was produced by atrial pacing in dogs with stenoses of the left anterior descending coronary artery that abolished reactive hyperemia to a ten-second coronary occlusion.[57] Pacing caused a twofold increase in blood flow in the left circumflex territory but produced no significant change in the left anterior descending coronary artery territory. Similarly, consumption of oxygen, glucose and free fatty acids remained unchanged from control, whereas extraction of lactate in control converted to net production during pacing and indicated the occurrence of metabolic ischemia.

Blood flow was evaluated with ammonia labeled with nitrogen 13, fatty acid metabolism with palmitate labeled with carbon 11 and the use of exogenous glucose with fluoro-2-deoxyglucose (FDG) 18. Intravenously administered ammonia $^{13}N$ distributes in myocardium in proportion to blood flow. Severe biochemical abnormalities can interfere with the metabolic trapping of this tracer[58,59] and could therefore offset the relationship between tracer tissue uptake and blood flow. The effects, however, of less severe abnormalities on the retention fraction of this tracer in myocardium are small and do not significantly alter the relationship between tracer uptake and blood flow in myocardium.

$^{18}FDG$, a glucose analogue, traces transmembranous glucose transport phosphorylation of glucose to glucose-6-phosphate. Because it is a poor substrate for glycogen synthesis, for glycolysis and the fructose-pentose shunt and because it is impermeable to the cell membrane, the phosphorylated $^{18}FDG$, such as, $^{18}FDG$-6-phosphate, accumulates in myocardium. Regional $^{18}FDG$ activity concentrations at 40 to 60 minutes after intravenous administration, therefore, represent regional rates of exogenous glucose use.[60,61] The use of palmitate $^{11}C$ as a tracer of myocardial fatty acid metabolism was based on extensive experimental work done by the group at Washington University (St Louis) and in our laboratory.[62,63] Bergmann and co-workers recently extensively reviewed their experimental findings with this tracer and critically assessed its virtues and shortcomings for evaluating regional myocardial fatty acid metabolism.[62]

Figure 4 shows PET images in one of these experiments of acute myocardial ischemia in dogs. Relative to control myocardium, blood flow is greatly reduced in the anterior wall. The serial PET images show uptake and subsequent clearance of palmitate $^{11}C$ in the corresponding cross section of the heart. After clearance of tracer from blood (at about three to five minutes), uptake of palmitate $^{11}C$ in myocardium as seen in proportion to blood flow is sharply reduced in the left anterior descending coronary artery territory. The progressively declining palmitate $^{11}C$ activity in myocardium is depicted on the following serial PET images and indicates clearance of tracer from myocardial tissue.

Tissue time-activity curves generated from regions of interest assigned to the left ventricular myocardium on the serial PET images permitted a more detailed analysis of tracer uptake and clearance. Figure 5 depicts two regional time-activity curves. One was obtained from normal and the other from acutely ischemic myocardium. The biexponential clearance pattern, which is seen best on the time-activity curve in normal myocardium, indicates that palmitate $^{11}C$ distributes in myocardium between at least two metabolic pools. They differ in size and have different turnover rates. The distribution of tracer in tissue seems consistent with the known metabolic rate of free fatty acid in myocardium as outlined schematically in Figure 6.[64] Long-chain free fatty acid is activated in myocardium to acyl-coenzyme A (CoA), which then proceeds along two different pathways. One fraction enters the large and slow turnover pool of endogenous lipid, composed largely of acylglycerides and phospholipids. The other fraction proceeds via the carnitine shuttle to the inner mitochondrial membrane where $\beta$-oxidation cleaves off the long-chain acyl-CoA units to two-carbon fragments, which then enter the tricarboxylic acid cycle in the form of acetyl-CoA as the final oxidative pathway.

Liedtke[55] and Neely and co-workers[56] have referred to $\beta$-oxidation as the locus most sensitive to inadequate oxygen availability. There is considerable experimental evidence in support of the $^{11}C$ clearance curve morphology as an accurate reflection of the metabolic fate of free fatty acid through these

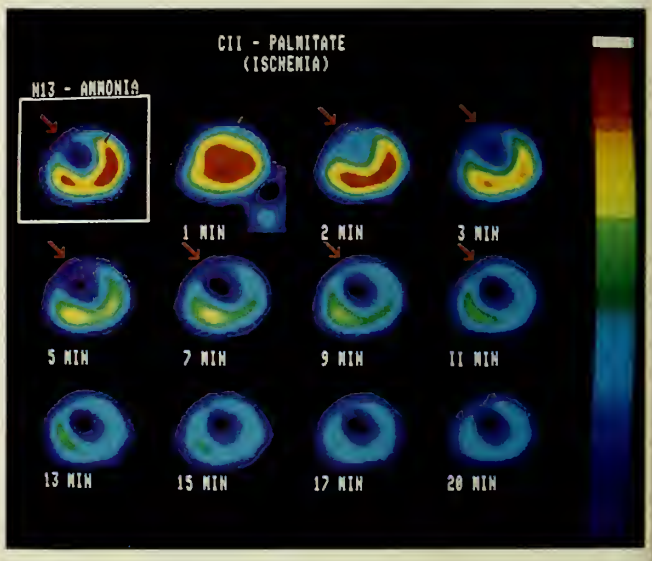



**Figure 4.**—Cross-sectional positron emission tomography (PET) images of regional myocardial blood flow (the use of ammonia-labeled nitrogen 13 is shown in upper left-hand corner) and of regional myocardial uptake and clearance of palmitate-labeled carbon 11 in an experiment of pacing-induced acute segmental myocardial ischemia in a dog. Serial PET imaging commenced with intravenous administration of palmitate $^{11}C$ ; the initial images were recorded at 1-minute intervals, the later images at 3-minute intervals. Early posttracer-injection images are determined by activity in the left ventricular blood pool. After clearance of tracer from blood, the myocardium is seen (at 3 min) and segmentally reduced uptake of tracer in the anterior wall is noted **(arrows)**. Compared with the image using ammonia $^{13}N$, myocardial uptake of palmitate $^{11}C$ largely parallels blood flow. The progressively declining intensity of the subsequent images indicates clearance of $^{11}C$ activity from myocardium.

*Professor of Radiological Sciences, Division of Nuclear Medicine and Biophysics, Department of Radiological Sciences, UCLA School of Medicine.

two major pathways. Although factors that account for the size and slope of the late slow clearance phase remain less well characterized, the relations between size and slope of the early clearance curve component and the fraction of palmitate $^{11}$C that enters oxidative pathways and its rate of oxidation are well established. The impairment of β-oxidation during acute myocardial ischemia is reflected by changes of the early clearance curve component.

In Figure 5, about 60% of the tracer enters the small and rapid-turnover oxidation pool in control myocardium and clears with a half-life of about eight minutes. In the acutely ischemic segment, however, only 27% of the tracer enters this pool and clears from it at a much slower rate as indicated by the 20-minute half-life. Consistent with the known impairment of β-oxidation, palmitate $^{11}$C proceeds through oxidation at a slower rate; accordingly, palmitate $^{11}$C is transferred less rapidly into mitochondria. Trapping of tracer by the endogenous lipid pool becomes more competitive with transport into mitochondria, and disproportionately more palmitate $^{11}$C is diverted into this slow turnover pool. The tissue time-activity curve reflects these changes. Relative size and clearance rates decreased whereas the relative size of the late, slow component of the clearance curve increased.

Similar, although less dramatic, changes of tissue clearance curve morphology can be shown in human myocardium during acute myocardial ischemia. Figure 7 is from a series of ten patients with arteriographically documented coronary artery disease who were studied in our laboratory.[65] Segmental myocardial uptake and clearance of palmitate $^{11}$C was determined by serial PET imaging initially at control and then again during moderate atrial pacing. Tissue clearance kinetics of palmitate $^{11}$C are compared for myocardium supplied by a normal circumflex and a stenosed (more than 70% diameter narrowing) anterior descending coronary artery. At control, clearance of palmitate $^{11}$C from both segments is virtually identical, suggesting normal fatty acid metabolism in myocardium supplied by the stenosed coronary artery. Moderate pacing failed to produce electrocardiographic changes but caused abnormal wall motion in the segment supplied by the stenosed vessel. An important point is that the regional response in palmitate $^{11}$C tissue kinetics to increased heart rates and, hence, to higher oxygen demand differed between the two segments. The relative size and the clearance rate of the early, rapid component of the clearance curve are high in normal myocardium and reflect more oxidation of free fatty

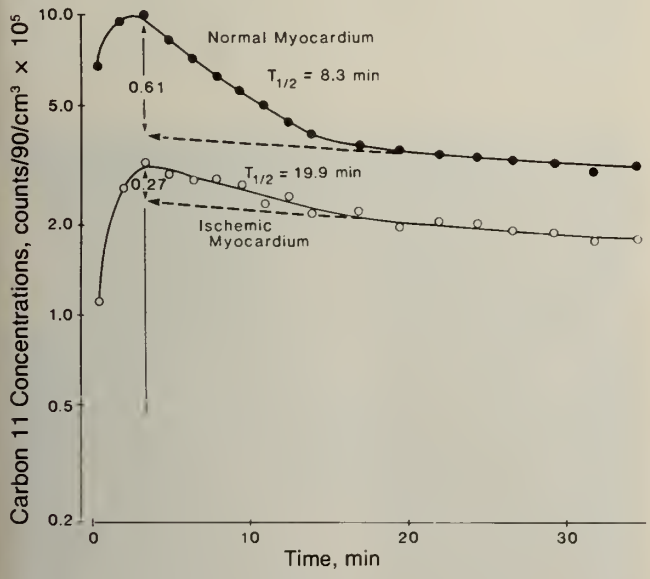



**Figure 5.**—The figure shows segmental myocardial uptake and clearance of palmitate labeled with carbon 11 in normal and acutely ischemic myocardium of the dog shown in Figure 4. The two time-activity curves were derived from regions of interest assigned to normal and acutely ischemic myocardium on the serial positron emission tomography images. Myocardial uptake is maximum at about 3 minutes after tracer injection and considerably lower in ischemic than in normal myocardium. Note the biexponential clearance pattern, indicating distribution of tracer in tissue between at least two metabolic pools that differ in size and turnover rate. About 6% of tracer enters in normal myocardium, the early rapid turnover pool, and clears with a half-life ($T_{½}$) of 8.3 minutes. The relative size and slope of this clearance curve component are related to the fraction of free fatty acid that is oxidized and the rate of oxidation. Both curves are greatly decreased in acutely ischemic myocardium and indicate reduced fatty acid oxidation.

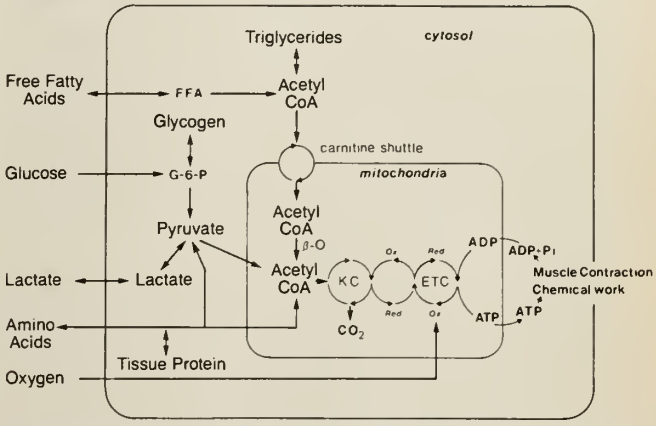



**Figure 6.**—The schematic representation shows myocardial substrate metabolism (from Schelbert[64]). β-O. = β-oxidation, CoA = coenzyme A, E.T.C. = electron transport change, FFA = free fatty acid, G-6-P = glucose-6-phosphate, K.C. = Krebs' or tricarboxylic acid cycle

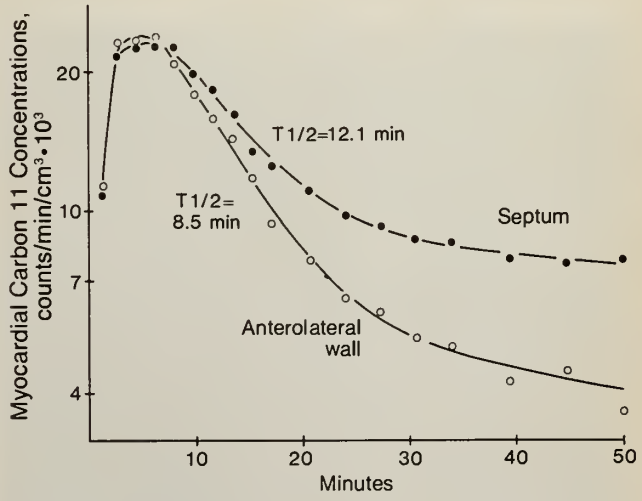



**Figure 7.**—Segmental myocardial clearance of palmitate labeled with carbon 11 in acute pacing-induced myocardial ischemia in a patient with coronary artery disease. The time-activity curves were obtained from serial positron emission tomography images recorded during moderate atrial pacing. Relative to normal myocardium (anterolateral wall), less tracer enters the rapid-turnover curve component and clears less rapidly (half-life [$T_{½}$] = 12.1 minutes as compared with 8.5 minutes in normal myocardium) in myocardium supplied by a stenosed coronary artery. The differences between the segmental tracer clearance curve morphology are similar to those observed in the dog experiment (Figure 5) and indicate a relative segmental decrease in oxidation of free fatty acid in the acutely ischemic segment.

acid (Figure 7). Myocardium supplied by a stenosed coronary artery shows similar directional changes, yet their magnitude is less. Thus, with increased cardiac work, tracer clearance from myocardium becomes heterogeneous. If, in the territory of the stenosed coronary artery, the increase in oxygen demand due to atrial pacing was not met by an appropriate increase in oxygen supply, mild ischemia ensued and prompted the inadequate response in oxidation of fatty acid. Such relative impairment in free fatty acid oxidation due to an acute supply-demand imbalance of oxygen can then be shown noninvasively in human myocardium with PET.

Glycolysis is another important part of the heart's substrate metabolism, which is also profoundly affected by myocardial ischemia. During the initial state of ischemia, flux of glucose through the glycolytic pathway increases.[55,56] This increase may persist when ischemia is mild.[66] The mechanisms regulating the widely documented shift from free fatty acid to carbohydrate use during ischemia remain speculative. Similarly unclear is whether the increase in glycolytic flux involved only anaerobic glycolysis, with pyruvate released as lactate from myocardium, or whether transfer of pyruvate into mitochondria for oxidation continues, at least in mild states of ischemia (Figure 6). Experiments in dogs, described earlier, showed that enhanced glycolytic flux can be observed noninvasively with PET during ischemia.[67]

Figure 8 is an example of one dog experiment. On the three contiguous cross-sectional images obtained with ammonia $^{13}N$, blood flow in the anterior wall (for example, left anterior descending coronary artery territory) is reduced relative to normal myocardium. Exogenous glucose use, however, is enhanced as seen on the corresponding $^{18}FDG$ images. This particular dog was studied after a 48-hour fasting period to elevate plasma free fatty acid levels and to promote free fatty acid as the major substrate in control myocardium while suppressing glucose use. Thus, the use of exogenous glucose was minimal in normal myocardium, as evidenced by the absence of $^{18}FDG$ uptake on the PET images, but dramatically increased in the relatively underperfused segment. Under less extreme conditions of substrate metabolism, the use of glucose usually varies in normal myocardium. Consequently, $^{18}FDG$ accumulates also in control myocardium.

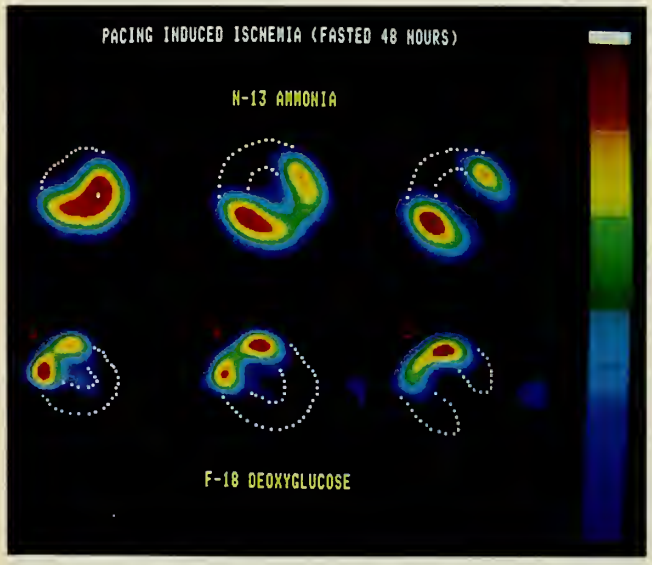



**Figure 8.**—Increased exogenous glucose use during acute pacing-induced myocardial ischemia in a dog is shown by positron emission tomography. The images on the top show three continuous cross-sections of blood flow (using ammonia labeled with nitrogen 13) and the images at the bottom show exogenous glucose uptake (using fluoro-2-deoxyglucose 18) in the corresponding cross-sections. Note the enhanced F-18 deoxyglucose uptake **(arrows)** in the anterior wall in which blood flow is reduced.

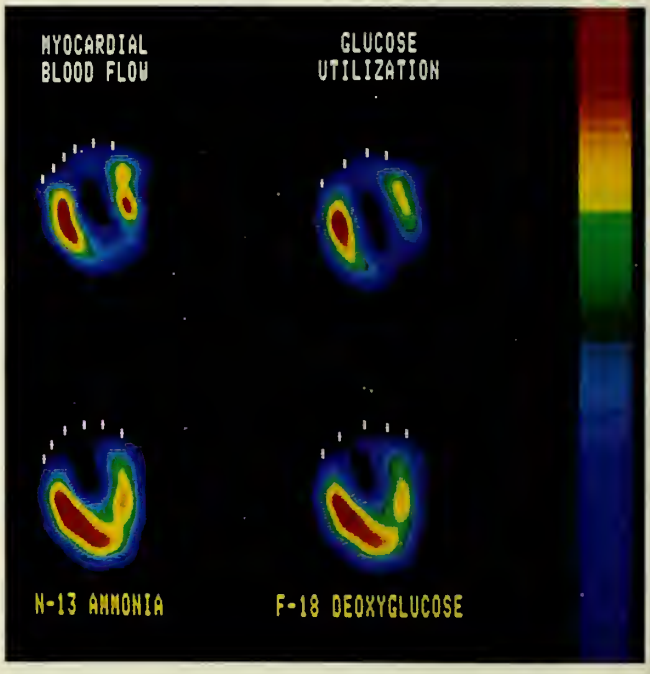



**Figure 9.**—Two contiguous cross-sectional positron emission tomography images of regional myocardial blood flow (left; ammonia labeled with nitrogen 13) and exogenous glucose use (right; fluoro-2-deoxyglucose 18) in a patient with ischemic heart disease. Note the reduced blood flow in the anterior wall associated with a proportionate segmental decrease in glucose use. The pattern is referred to in the text as "concordantly reduced tracer uptake."

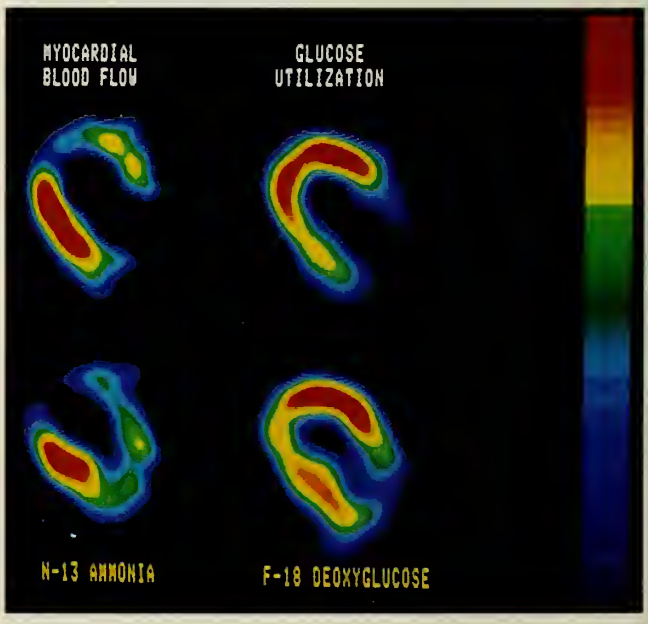



**Figure 10.**—Two contiguous cross-sectional positron emission tomography images of regional myocardial blood flow (left; ammonia labeled with nitrogen 13) and exogenous glucose use (right; fluoro-2-deoxyglucose 18) in a patient with ischemic heart disease. Note the enhanced F-18 deoxyglucose uptake in the anterior wall and in the interventricular septum. Both segments reveal greatly reduced blood flow on the N-13 ammonia images. This pattern is referred to in the text as "discordant tracer uptake" and is similar to that seen in the dog experiment shown in Figure 8.

Tracer uptake in ischemic myocardium is then only relatively increased when compared with blood flow—that is, it may be the same or even less than in control myocardium—but greatly exceeds blood flow in ischemic myocardium. Thus, ischemia-related enhanced glycolytic flux can be shown noninvasively with PET in the form of either an absolute or a relative increase in segmental tracer accumulation.[67]

Similar changes can be shown with PET in patients. Camici and colleagues subjected patients to supine bicycle exercise and evaluated regional myocardial blood flow with the use of rubidium 82 at rest, during and immediately after exercise.[68] Use of the positron-emitting cation $^{82}$Rb had been proposed by Budinger and associates as a tracer of blood flow suitable for PET imaging.[69] Like the earlier mentioned ammonia $^{13}$N, biochemical alterations can affect the myocardial retention of this tracer, although the magnitude of these effects is relatively small.[70] In the studies by Camici and coworkers, exercise-induced new perfusion abnormalities were seen as segmentally reduced $^{82}$Rb uptake. $^{18}$FDG, when injected during exercise, accumulated in the segment with decreased $^{82}$Rb uptake in excess of blood flow and thus was relatively increased. When administered 10 to 15 minutes after exercise and after resolution of transient blood flow reductions, $^{18}$FDG accumulated only in the previously ischemic segments. A decline in glucose use in normal myocardium from rest to exercise probably accounted for this difference between relatively and absolutely increased uptake between the two study conditions. The relative increase in $^{18}$FDG uptake during exercise was most likely caused by a relative increase in glycolytic flux in acutely ischemic myocardium. On the other hand, several mechanisms may account for the increased uptake in postischemic myocardium. Replenishment of glycogen stores, which were depleted during exercise, may be one explanation, while persistence of metabolic disturbance for some time after the acute ischemic episode may be another one.[71] The existence of such mechanisms seems to be supported by studies in isolated perfused hearts and in long-term experiments in dogs where fatty acid metabolism remained depressed for some time after reperfusion and was paralleled by increased $^{18}$FDG uptake.[72]

Relative or absolute increases in segmental $^{18}$FDG uptake are frequently seen on PET in patients with ischemic heart disease who were asymptomatic at the time of or during the 24- to 48-hour period preceding the study (Figures 9 and 10). In Figure 9, ammonia $^{13}$N and $^{18}$FDG uptake are concordingly decreased. In the other patient (Figure 10), tracer uptake is discordant. The $^{18}$FDG uptake is normal, or even mildly increased, in the underperfused anterior and anteroseptal regions of the myocardium. The mechanisms underlying these patterns remain to be elucidated. The discordant tracer uptake may reflect persistence of metabolic abnormalities in post ischemic myocardium. It also could reflect a metabolic adjustment to a long-term low oxygen state. Clarification of these mechanisms is important because they could provide new insights into the pathophysiology of myocardial ischemia.

From a clinical perspective, the tracer pattern might reflect the presence of tissue viability. To examine this possibility, we studied patients with segmental wall-motion abnormalities who were scheduled for a coronary artery bypass procedure.[73] Segmental myocardial function was determined before and six to eight weeks after surgical revascularization. The PET studies were done with ammonia $^{13}$N and $^{18}$FDG. In a total of 73 segments with impaired wall motion, PET showed preserved or enhanced $^{18}$FDG uptake in 63%, whereas it was decreased in proportion to blood flow in the other 37% of segments. Only 8% of the latter segments showed a functional improvement after the operation as compared with a functional improvement in 82% of segments with preserved or enhanced $^{18}$FDG uptake before the operation. This functional improvement in these segments indicates that preserved or enhanced $^{18}$FDG uptake in segments with decreased blood flow and impaired function identifies tissue that is viable and will benefit from surgical revascularization. This pattern predicted, with a 92% accuracy, the effects of surgical revascularization on segmental myocardial function.

Other more recent studies compared this pattern on PET with conventional indices of regional myocardial blood flow, function and tissue viability. For example, in 68% of segments with Q waves on electrocardiogram, glucose use was preserved or even enhanced.[74] These segments were defined as "PET ischemic" as compared with "PET infarcted" segments in which blood flow and glucose use were concordantly decreased. The degree of functional impairment on wall motion was similar for both types of segments. Wall-motion scores did not differ significantly between "PET ischemic" and "PET infarcted" segments. Residual blood flow seems important for maintaining, at least to some extent, metabolic activity. Intracellular accumulation of lactic acid together with hydrogen ions inhibits glycolysis. If both are removed from ischemic myocardium through residual blood flow, anaerobic glycolysis can be maintained. There was, indeed, a significant correlation between residual tissue blood flow (as observed on the cross-sectional PET images of the ammonia $^{13}$N distribution) and increased $^{18}$FDG uptake. In spite of the absence of ammonia $^{13}$N uptake in 32% of abnormal segments, however, $^{18}$FDG uptake was present. Although some residual blood flow may have been present in these segments, it could not be detected or appreciated on the cross-sectional blood flow images. Finally, complete or partial resolution of exercise-induced defects on scintigraphy using thallium 201 is considered an index of tissue viability. Comparative studies in our laboratory were in agreement with these findings.[75] Myocardial segments that showed resolving perfusion abnormalities on $^{201}$Tl scintigraphy had enhanced or normal $^{18}$FDG uptake on PET. Of segments with fixed $^{201}$Tl defects, however, suggesting irreversible tissue injury, 58% were either normal or ischemic on PET. Therefore, although defect resolution on $^{201}$Tl scintigraphy reliably indicates tissue viability, fixed defects, on the other hand, overestimate the incidence of tissue necrosis. Residual metabolic activity and, thus, tissue viability in these segments are identified more reliably with a metabolic marker and PET.

A similar pattern, such as enhanced or preserved $^{18}$FDG uptake in segments with reduced blood flow, is also seen in patients during the subacute phase of a myocardial infarction (Figure 11).[76] There are Q waves in the anteroseptal leads on the patient's electrocardiogram, and blood flow is greatly reduced in the anterior wall as seen on the cross-sectional ammonia $^{13}$N images taken 52 hours after the abrupt onset of symptoms. Substantially enhanced glucose use in the same area on the corresponding cross-sectional $^{18}$FDG images indicates the persistence of metabolic activity. Increased glucose use probably reflects increased glycolytic flux, either partially or completely anaerobic. The palmitate $^{11}$C images taken two days later show residual fatty acid metabolism. Tracer uptake

is reduced in proportion to blood flow. Retention of tracer—that is, greatly delayed clearance in infarcted segments—suggests that the initial metabolic steps of activation of long-chain fatty acid to acyl-CoA remained operational, whereas the relative increase in $^{11}C$ activity concentrations in injured myocardium on the late images suggests impaired oxidation of tracer, which then is deposited in the endogenous lipid pool. Clearance of tracer in the infarcted segment differs considerably from that in presumably normal myocardium. The $^{11}C$ activity is no longer seen on the late images, suggesting normal or rapid oxidation of tracer and, hence, normal or even enhanced free fatty acid oxidation.

To examine the significance of the preserved segmental metabolic activity early after acute myocardial infarction on functional outcome, 12 patients were studied.[76] In a total of 29 segments with reduced blood flow, $^{18}FDG$ uptake was reduced or absent in 41%. When examined six to eight weeks later, function in these segments remained depressed or had deteriorated even further. On the other hand, 17 segments (59%) were associated early after infarction with preserved or enhanced glucose use. The functional outcome in these segments was variable; in about 50% function improved spontaneously, which was associated with improved regional myocardial blood flow and normalization of $^{18}FDG$ uptake (Figure 10). By contrast, no change in function, or even further deterioration, was noted in the other half, despite persistence of metabolic activity early after the initial event. This was associated with a loss of metabolic activity over time in patients who were restudied with PET. Preservation of metabolic activity early after infarction may be due to residual tissue blood flow antegradedly through a partially obstructed coronary artery, or through collaterals, or both.[77] In other instances, it also may be due to restoration of adequate blood flow either through recanalization of the infarcted vessel or opening of collaterals. The two latter mechanisms could explain the spontaneous improvement in segmental function. Development of criteria that will accurately predict in which segments function will, or will not, recover spontaneously would establish a rationale for immediate intervention with restoration of blood flow during the early postinfarction period.

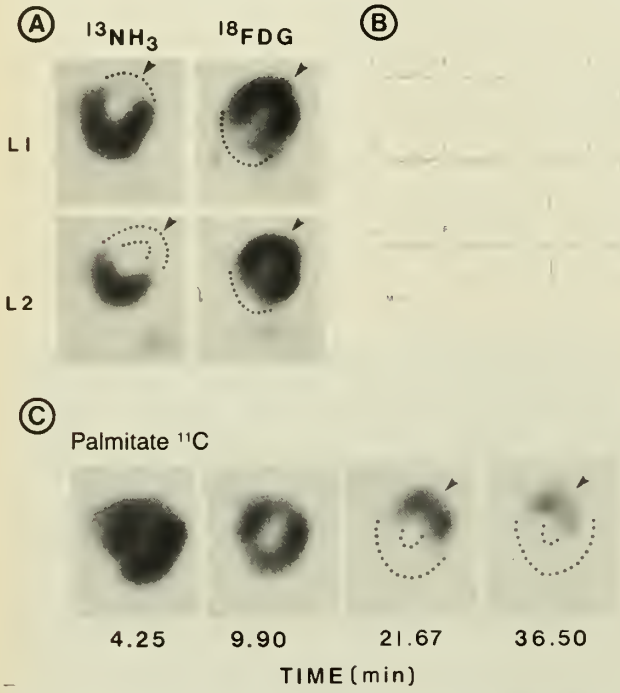



**Figure 11.**—Blood flow, glucose and fatty acid metabolism are shown in a patient studied with positron emission tomography (PET) during the subacute phase of an acute myocardial infarction. The electrocardiogram (**B**, upper right panel) shows Q waves in the anteroseptal leads. The two contiguous images (**L1** and **L2**) of blood flow (molecular hydrogen labeled with nitrogen 13 [$^{13}NH_3$]) and glucose uptake fluoro-2-deoxyglucose (FDG) 18 images (**A**, upper left panel) were taken 52 hours after the abrupt onset of symptoms and showed decreased blood flow and increased glucose use in the infarcted anterior wall. The lower panel (**C**) shows selected serial PET images after administration of palmitate labeled with carbon 11. Reduced tracer uptake is seen on the early images in the anterior wall; while tracer clears rapidly from normal myocardium, it is retained by the infarcted segment as evidenced by the increased uptake on the late images. This augmented retention of tracer is consistent with impaired fatty acid oxidation in the infarcted segment that also shows augmented exogenous glucose use.

In his introductory remarks, Dr Langer described the distribution of high-energy phosphate expenditure between various cell functions. The major share goes to the development of tension, fiber shortening and contractility. Dr Langer also referred to a sequence of events that occurs when oxygen supply becomes inadequate. Diastolic relaxation, systolic tension development and fiber shortening are abandoned first. Residual production of high-energy phosphate is used for protecting the cell's integrity and viability. Although inefficient, this can, to some extent, be accomplished by ATP production through anaerobic means, as Dr Weiss pointed out. For what time periods this last resort of ATP production can be maintained will depend on residual blood flow for removing metabolic intermediates, such as lactic acid and hydrogen ions, which otherwise would inhibit glycolysis. Therefore, evaluation of regional myocardial function or of residual blood flow is inadequate to gauge accurately the severity of ischemia. A direct assessment of metabolic activity in ischemically compromised tissue will identify more accurately whether cellular integrity is maintained. Enhanced glucose use observed with PET in various states of ischemia in the absence of mechanical function or appreciable blood flow is in line with this notion. Beyond this, the mere number of positron tracers of other metabolic pathways, such as tricarboxylic acid cycle activity or amino acid metabolism and its role in energy metabolism, offers new possibilities for exploring human myocardial ischemia. The simultaneous use of several such tracers as a novel and unique capability of PET in the future will not only provide one piece of the jigsaw puzzle of metabolism in ischemia but will permit the piecing together of various aspects of metabolic compromise in ischemia. They will improve our understanding of the pathophysiology of human myocardial ischemia with respect to its dynamic nature and should have an impact on diagnostic and therapeutic acuity.

#### REFERENCES

1. Heart Facts. Dallas, American Heart Association, 1984, p3
2. Kobayashi K, Neely JR: Control of maximum rates of glycolysis in rat cardiac muscle. Circ Res 1979; 44:166-175
3. Berne RM, Knabb RM, Ely SW, et al: Adenosine in the local regulation of blood flow: A brief overview. Fed Proc 1983; 42:3136-3142
4. Gibbs CL, Chapman JB: Cardiac energetics, *In* Berne RM, Sperelakis N, Geiger S (Eds): Handbook of Physiology—The Cardiovascular System. Bethesda, Md, American Physiological Society, 1979, pp 775-804
5. Shine KI, Douglas AM, Ricchiuti N: Ischemia in isolated interventricular septa: Mechanical events. Am J Physiol 1976; 231:1225-1232
6. Weiss J, Shine KI: Extracellular $K^+$ accumulation during myocardial ischemia in isolated rabbit heart. Am J Physiol 1982; 242:H619-H628
7. Kleber AG: Extracellular potassium accumulation in acute myocardial ischemia. J Mol Cell Cardiol 1984; 16:389-394
8. Hearse DJ, Garlick PB, Humphrey SM: Ischemic contracture of the myocardium: Mechanisms and prevention. Am J Cardiol 1977; 39:986-993

9. Rau EE, Shine KI, Langer GA: Potassium exchange and mechanical performance in anoxic mammalian myocardium. Am J Physiol 1977; 232:H85-H94
10. Goldman L, Cook F, Hashimoto B, et al: Evidence that hospital care for acute myocardial infarction has not contributed to the decline in coronary mortality between 1973-1974 and 1978-1979. Circulation 1982; 65:936-942
11. Hauser AM, Gangadharan V, Ramos RG, et al: Sequence of mechanical, electrocardiographic and clinical effects of repeated coronary artery occlusion in human beings: Echocardiographic observations during coronary angioplasty. J Am Coll Cardiol 1985; 5:193-197
12. Jennings RB, Reimer KA: Factors involved in salvaging ischemic myocardium: Effect of reperfusion of arterial blood. Circulation 1983; 68(pt 2):125-36
13. El-Sherif N, Scherlag BJ, Lazzara R: Electrode catheter recordings during malignant ventricular arrhythmia following experimental acute myocardial ischemia. Circulation 1975; 51:1003-1014
14. Janse MJ, Van Capelle FJL, Morsink H, et al: Flow of 'injury' current and patterns of excitation during early ventricular arrhythmias in acute regional myocardial ischemia in isolated porcine and canine hearts. Circ Res 1980; 47:151-165
15. Witt AL, Bigger JT Jr: Possible electrophysiological mechanisms for lethal arrhythmias accompanying myocardial ischemia and infarction. Circulation 1975; 51,52(suppl III):III96-III115
16. Harris AS, Bisteni A, Russell RA, et al: Excitatory factors in ventricular tachycardia resulting from myocardial ischemia: Potassium a major excitant. Science 1954; 119:200-203
17. Morena H, Janse MJ, Fiolet JWT, et al: Comparison of the effects of regional ischemia, hypoxia, hyperkalemia, and acidosis on intracellular and extracellular potentials and metabolism in the isolated porcine heart. Circ Res 1980; 46:634-646
18. Weiss J, Shine KI: $[K^+]_o$ accumulation and electrophysiological alterations during early myocardial ischemia. Am J Physiol 1982; 243:H318-H327
19. Wiegand V, Guggi M, Meesmann W, et al: Extracellular potassium activity changes in the canine myocardium after acute coronary occlusion and the influence of beta-blockade. Cardiovasc Res 1979; 13:297-302
20. Hill JL, Gettes LS: Effect of acute coronary artery occlusion on local myocardial extracellular $K^+$ activity in swine. Circulation 1980; 61:768-778
21. Hirche HJ, Franz CHR, Bös L, et al: Myocardial extracellular $K^+$ and $H^+$ increase and noradrenaline release as possible cause of early arrhythmias following acute coronary artery occlusion in pigs. J Mol Cell Cardiol 1980; 12:579-593
22. Shine KI, Douglas AM, Ricchiuti N: $^{42}K$ exchange during myocardial ischemia. Am J Physiol 1977; 232:H564-H570
23. Kleber A: Resting membrane potential, extracellular $K^+$ activity, and intracellular $Na^+$ activity during global ischemia in isolated perfused guinea pig hearts. Circ Res 1983; 52:442-450
24. Isenberg G, Vereecke J, van der Heyden G, et al: The shortening of the action potential by DNP in guinea-pig ventricular myocytes is mediated by an increase of a time-independent K conductance. Pflügers Arch 1983; 397:251-259
25. Noma A: ATP regulated $K^+$ channels in cardiac muscle. Nature 1983; 305:147-148
26. Trube G, Hescheler J: Inward-rectifying channels in isolated patches of heart cell membrane: ATP-dependence and comparison with cell-attached patches. Pflügers Arch 1984; 401:178-184
27. Kakei M, Noma A, Shibasaki T: Properties of adenosine-triphosphate-regulated potassium channels in guinea-pig ventricular cells. J Physiol (Lond) 1985; 363:441-462
28. McDonald TF, MacLeod DP: Metabolism and the electrical activity of anoxic ventricular muscle. J Physiol (Lond) 1973; 229:559-582
29. Bricknell OL, Opie LH: Effects of substrates on tissue metabolic changes in the isolated rat heart during underperfusion and on release of lactate dehydrogenase and arrhythmias during reperfusion. Circ Res 1978; 43:102-115
30. Higgins TJC, Bailey PJ, Allsopp D: Interrelationship between cellular metabolic status and susceptibility of heart cells to attach by phospholipase. J Mol Cell Cardiol 1982; 14:645-654
31. Hasin Y, Barry WH: Myocardial metabolic inhibition and membrane potential, contraction, and potassium uptake. Am J Physiol 1984; 247:H322-H329
32. Weiss J, Hiltbrand B: Functional compartmentation of glycolytic versus oxidative metabolism in isolated rabbit heart. J Clin Invest 1985; 75:436-447
33. Saman S, Opie LH: Mechanism of reduction of action potential duration of ventricular myocardium by exogenous lactate. J Mol Cell Cardiol 1984; 16:659-662
34. Corr PB, Gross RW, Sobel BE: Amphipathic metabolites and membrane dysfunction in ischemic myocardium. Circ Res 1984; 55:135-154
35. Clarkson CW, Ten Eick RE: On the mechanism of lysophosphatidylcholine-induced depolarization of cat ventricular myocardium. Circ Res 1983; 52:543-556
36. Weiss J, Couper GS, Hiltbrand B, et al: Role of acidosis in early contractile dysfunction during ischemia: Evidence from $pH_0$ measurements. Am J Physiol 1984; 247(pt 2):H760-H767
37. Hess ML, Manson NH: Molecular oxygen: Friend and foe—The role of the oxygen free radical system in the calcium paradox, the oxygen paradox and ischemia/reperfusion injury. J Mol Cell Cardiol 1984; 16:969-985
38. Barrington PL, Meier CF, Dickens BF, et al: Free radical scavengers protect canine myocytes from free radical-induced changes in the action potential (Abstr). Circulation 1985; 72(suppl III):III228
39. Bernier M, Hearse DJ, Manning AS: Reperfusion-induced arrhythmias and oxygen-derived free radicals. Circ Res 1986; 58:331-340
40. Jacobus WE, Pores IH, Lucas SK, et al: Intracellular acidosis and contractility in the normal and ischemic heart as examined by $^{31}P$ NMR. J Mol Cell Cardiol 1982; 14(suppl 3):13-20
41. Kübler W, Katz AM: Mechanism of early 'pump' failure of the ischemic heart: Possible role of adenosine triphosphate depletion and inorganic phosphate accumulation. Am J Cardiol 1977; 40:467-471
42. Allen DG, Orchard CH: Measurements of intracellular calcium concentration in heart muscle: The effects of inotropic interventions and hypoxia. J Mol Cell Cardiol 1984; 16:117-128
43. Nayler WG, Poole-Wilson PA, Williams A: Hypoxia and calcium. J Mol Cell Cardiol 1979; 11:683-706
44. Kammermeier H, Schmidt P, Jüngling E: Free energy change of ATP-hydrolysis: A causal factor of early hypoxic failure of the myocardium? J Mol Cell Cardiol 1982; 14:267-277
45. Gudbjarnason S, Mathes P, Ravens KG: Functional compartmentation of ATP and creatine phosphate in heart muscle. J Mol Cell Cardiol 1970; 1:325-339
46. Jacobus WE: Respiratory control and the integration of heart high-energy phosphate metabolism by mitochondrial creatine kinase. Annu Rev Physiol 1985; 47:707-725
47. Bricknell OL, Daries PS, Opie LH: A relationship between adenosine triphosphate, glycolysis and ischemic contracture in the isolated rat heart. J Mol Cell Cardiol 1981; 13:941-945
48. Parker JC, Hoffman JF: The role of membrane phosphoglycerate kinase in the control of glycolytic rate by active cation transport in human red blood cells. J Gen Physiol 1967; 50:893-916
49. Paul RJ: Functional compartmentalization of oxidative and glycolytic metabolism in vascular smooth muscle. Am J Physiol 1983; 244:C399-C409
50. Fogelman AM, Abbasi AS, Pearce ML, et al: Echocardiographic study of the abnormal motion of the posterior left ventricular wall during angina pectoris. Circulation 1972; 46:905-913
51. Clusin WT: Do caffeine and metabolic inhibitors increase free calcium in the heart?—Interpretation of conflicting intracellular calcium measurements. J Mol Cell Cardiol 1985; 17:213-220
52. Lipasti JA, Nevalainen TJ, Alanen KA, et al: Anaerobic glycolysis and the development of ischaemic contracture in isolated rat heart. Cardiovasc Res 1984; 18:145-148
53. Entman ML, Kaniike K, Goldstein MA, et al: Association of glycogenolysis with cardiac sarcoplasmic reticulum. J Biol Chem 1976; 251:3140-3146
54. Neely JR, Grotyohann LW: Role of glycolytic products in damage to ischemic myocardium. Circ Res 1984; 55:816-824
55. Liedtke AJ: Alterations of carbohydrate and lipid metabolism in the acutely ischemic heart. Prog Cardiovasc Dis 1981; 23:321-336
56. Neely JR, Rovetto MJ, Oram JF: Myocardial utilization of carbohydrate and lipids. Prog Cardiovasc Dis 1972; 15:289-329
57. Schelbert HR, Henze E, Keen R, et al: C-11 palmitate for the noninvasive evaluation of regional myocardial fatty acid metabolism with positron-computed tomography—IV. In vivo evaluation of acute demand-induced ischemia in dogs. Am Heart J 1983; 106(pt 1):736-750
58. Schelbert HR, Phelps ME, Huang SC, et al: N-13 ammonia as an indicator of myocardial blood flow. Circulation 1981; 63:1259-1272
59. Bergmann SR, Hack S, Tewson T, et al: The dependence of accumulation of $^{13}NH_3$ by myocardium on metabolic factors and its implications for the quantitative assessment of perfusion. Circulation 1980; 61:34-43
60. Sokoloff L, Reivich M, Kennedy C, et al: The [$^{14}C$]-deoxyglucose method for the measurement of local cerebral glucose utilization: Theory, procedure and normal values in the conscious and anesthetized albino rat. J Neurochem 1977; 28:897-916
61. Ratib O, Phelps ME, Huang SC, et al: Positron tomography with deoxyglucose for estimating local myocardial glucose metabolism. J Nucl Med 1982; 23:577-586
62. Bergmann SR, Fox KAA, Geltman EM, et al: Positron emission tomography of the heart. Prog Cardiovasc Dis 1985; 28:165-194
63. Schelbert HR, Schwaiger M: PET studies of the heart, chap 12, *In* Phelps M, Mazziota J, Schelbert H (Eds): Positron Emission Tomography and Autoradiography: Principles and Applications for the Brain and Heart. New York, Raven Press, 1986, pp 581-661
64. Schelbert HR: The heart, *In* Ell PJ, Holman BL (Eds): Computed Emission Tomography. New York, Oxford University Press, 1982, pp 91-133
65. Grover-McKay M, Schelbert HR, Schwaiger M, et al: Identification of impaired metabolic reserve by atrial pacing in patients with significant coronary artery stenosis. Circulation 1986; 74:281-292
66. Opie LH, Owen P, Riemersma RA: Relative rates of oxidation of glucose and free fatty acids by ischemic and non-ischemic myocardium after coronary artery ligation in the dog. Eur J Clin Invest 1973; 3:419-435
67. Schelbert HR, Phelps ME, Selin C, et al: Regional myocardial ischemia assessed by $^{18}$fluoro-2-deoxyglucose and positron emission computed tomography, *In* Heiss HW (Ed): Advances in Clinical Cardiology—Quantification of Myocardial Ischemia, Vol 1. New York, Gehard Witzstrock Publishing, 1980, pp 437-447
68. Camici P, Araujo LI, Spinks T, et al: Increased uptake of $^{18}F$-fluorodeoxyglucose in postischemic myocardium of patients with exercise-induced angina. Circulation 1986; 74:81-88
69. Budinger TF, Yano Y, Derenzo SE, et al: Rb-82 myocardial positron emission tomography (Abstr). J Nucl Med 1979; 20:P603
70. Goldstein RA, Mullani NA, Marani SK, et al: Myocardial perfusion with rubidium-82—II. Effects of metabolic and pharmacologic interventions. J Nucl Med 1983; 24:907-915
71. Camici P, Bailey IA: Time course of myocardial glycogen repletion following acute transient ischemia. Circulation 1984; 70:11-85
72. Schwaiger M, Schelbert HR, Ellison D, et al: Sustained regional abnormalities in cardiac metabolism after transient ischemia in the chronic dog model. J Am Coll Cardiol 1985; 6:336-347
73. Tillisch J, Brunken R, Marshall R, et al: Reversibility of cardiac wall-motion abnormalities predicted by positron tomography. N Engl J Med 1986; 314:884-888
74. Brunken R, Tillisch J, Schwaiger M, et al: Regional perfusion, glucose metabolism and wall motion in chronic electrocardiographic Q-wave infarctions. Circulation 1986; 73:951-963
75. Brunken RC, Tillisch JH, Schwaiger M, et al: Positron emission tomography identifies viable tissue in myocardial segments with fixed thallium perfusion defects (Abstr). J Nucl Med 1986; 27:932-933
76. Schwaiger M, Brunken RC, Grover-McKay M, et al: Metabolic tissue characterization in patients with acute myocardial infarction with positron tomography (Abstr). J Nucl Med 1985; 26:P87
77. Schwaiger M, Brunken R, Tillisch J, et al: Tissue viability and coronary anatomy in patients with acute myocardial infarction (Abstr). Circulation 1985; 72:III392

# Peptic Ulcer Disease

## Pathophysiology and Current Medical Management

*These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs Homer A. Boushey, Associate Professor of Medicine, and David G. Warnock, Associate Professor of Medicine, under the direction of Dr Lloyd H. Smith, Jr, Professor of Medicine and Associate Dean in the School of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, School of Medicine, San Francisco, CA 94143.*

RICHARD K. ROOT, MD:* *It is a pleasure to introduce Dr Bruce Scharschmidt, who will discuss peptic ulcer disease, including current concepts of pathophysiology and medical management. Dr Scharschmidt is Professor of Medicine and has been recently selected as the new editor of the* Journal of Clinical Investigation, *the responsibility for which was transferred to the University of California, San Francisco (UCSF), campus in May 1987. He received his MD training at Northwestern University (Chicago, Ill) and served as a house officer at UCSF from 1970 through 1972. He subsequently spent three years at the National Institutes of Health and returned to UCSF for a fellowship in gastroenterology from 1975 through 1977, following which he was appointed to the faculty and rose rapidly to the professorial level. Besides his newly assumed editorship, he has recently finished a five-year term as associate editor of* Gastroenterology.

BRUCE F. SCHARSCHMIDT, MD:† Thank you, Dr Root. Given the huge literature on the topic of acid peptic disease and the large number of controlled trials that have been carried out in the past decade, one might assume that all of the important clinical questions would have been addressed and answered. In fact, this is not the case, and there remains lively debate on a number of points. In this conference I will not review the basic aspects of acid peptic disease, including the typical symptoms and approach to diagnosis, which are already well known to most physicians. Rather, I will focus on currently emerging concepts and controversies regarding the pathophysiology of acid peptic disease and various approaches to management.

### Pathophysiology

An acid peptic disorder occurs when the injurious effects of acid and pepsin overwhelm the mucosal barrier. It is helpful to visualize acid peptic disease in the form of a pseudoequation

$$\text{acid peptic disease} \propto \frac{\text{acid} + \text{pepsin}}{\text{mucosal barrier}}$$

where the likelihood of acid peptic disease developing is directly proportional to the amount of acid and pepsin produced and inversely proportional to the integrity of the mucosal barrier. In this context, certain disorders, such as the Zollinger-Ellison syndrome, represent disorders of the numerator. On the other hand, gastric ulcer disease and acute gastritis represent disorders in which the integrity of the mucosal barrier is impaired and ulceration occurs even though the amount of acid and pepsin produced is normal or subnormal. Moreover, one would anticipate that agents that are effective in healing or preventing ulcers do so by decreasing the numerator, increasing the denominator or both.[1] I will briefly discuss current concepts regarding the regulation of acid secretion and the mucosal barrier.

*Acid Secretion*

The parietal cell, which is present in oxyntic glands in the fundus and body of the stomach, is the source of gastric acid production. The parietal cell is the clear winner among all epithelial cells in its ability to generate a hydrogen ion concentration gradient. The pH in the gastric lumen is often as low as 1 to 2, as compared with a pH of 7.4 in blood. This 6-log concentration difference is much greater, for example, than the maximum hydrogen ion concentration difference between urine and blood. This remarkable ability of the parietal cell to create a steep pH gradient has attracted the attention of both basic scientists and clinical investigators, and there has been considerable recent progress in our understanding of how the parietal cell works and what regulates it.

*Morphology of the parietal cell.* With stimulation, the parietal cell undergoes a rather striking morphologic transformation.[2-5] In the resting state, the parietal cell is characterized by an abundant intracellular membranous tubulovesicular network. The interior of this tubulovesicular network is acidic, and certain agents such as omeprazole, which is useful in treating ulcer disease, accumulate in these highly acidic compartments, as will be discussed later. With stimulation, this membranous tubulovesicular network disappears and is replaced by an extensive intracellular canalicular network that is in direct communication with the lumen of the oxyntic gland and, in effect, tremendously amplifies the surface area of the apical membrane of the cell. This morphologic transformation is evident within 3 minutes of parietal cell stimulation, is complete in 30

*Professor and Chair, Department of Medicine, UCSF School of Medicine.
†Professor of Medicine, Department of Medicine and Liver Center, UCSF.

(Scharschmidt BF: Peptic ulcer disease—Pathophysiology and current medical management [Medical Staff Conference]. West J Med 1987 Jun; 146:724-733)

Supported in part by National Institutes of Health grants No. AM-26270 and No. AM-26743.

ABBREVIATIONS USED IN TEXT

cyclic AMP = adenosine 3′:5′-cyclic phosphate
$H^+$, $K^+$-ATPase = hydrogen and potassium ion adenosine triphosphatase
UCSF = University of California, San Francisco

minutes and is also completely reversible in 30 minutes. Current evidence suggests that this morphologic transformation represents fusion of these tubulovesicular structures with the apical membrane of the cell. This process of fusion delivers to the apical membrane the "acid" pump—that is, hydrogen and potassium ion adenosine triphosphatase ($H^+$, $K^+$-ATPase)—that actually mediates acid secretion (depicted schematically in Figure 1).[6] I might also mention that this mechanism for regulating secretion, which involves recruitment of pumps or carriers from cytoplasmic vesicles by a process of membrane fusion, was first identified in parietal cells and is now recognized to be a general mechanism for regulating transport. There is evidence, for example, that this is the mechanism by which the distal nephron regulates acidification of urine- and antidiuretic hormone-dependent water permeability, as well as the mechanism by which the adipocyte alters glucose transport in response to insulin.

*Regulation of acid secretion.* Various substances are known to stimulate the parietal cell to secrete acid. These include acetylcholine, histamine and gastrin, and current evidence suggests that the parietal cell has separate receptors for each of these secretagogues, as depicted in Figure 1.[2] Histamine is released from specialized mast cells in the

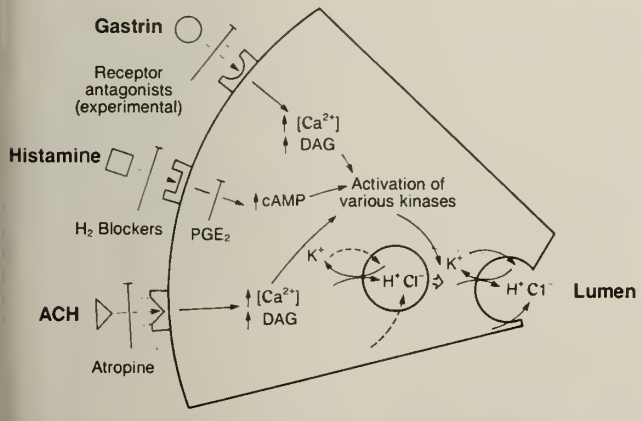



**Figure 1.**—Secretagogue-induced stimulation of gastric parietal cells. Current evidence suggests that the parietal cell has separate receptors for acetylcholine (ACH) (blocked by atropine), histamine (blocked by $H_2$-receptor antagonists) and gastrin. While gastrin-cholecystokinin receptor antagonists have been used in experimental studies, none are potent and selective enough to be useful clinically. Occupation and stimulation of the histamine receptor results in activation of adenylate cyclase and increased levels of adenosine 3′:5′-cyclic phosphate (cAMP), whereas current evidence suggests that ACH and gastrin stimulate phosphoinositide turnover and increase intracellular levels of diacyl glycerol (DAG) and $Ca^{2+}$. These second messengers (cAMP, $Ca^{2+}$, DAG) exert their effect, at least in part, by activation of various interacting protein kinases, which presumably phosphorylate key proteins within the parietal cell that trigger fusion of intracellular hydrogen and potassium ion-adenosine triphosphatase-containing vesicles with the apical plasma membrane, thereby increasing acid secretion. The mutually potentiating effects of these secretagogues may result from the interaction among the various protein kinases. $PGE_2$ = prostaglandin $E_2$

gastric mucosa and presumably diffuses to the parietal cell where it interacts with a specific receptor, the $H_2$ receptor. The interaction of histamine with the $H_2$ receptor is blocked by $H_2$-receptor antagonists such as cimetidine, ranitidine or famotidine. Stimulation of this receptor results in activation of adenylate cyclase and increased intracellular levels of adenosine 3′:5′-cyclic phosphate (cyclic AMP) that presumably trigger the cascade of events described above. It is also of interest that certain prostaglandins appear to interfere with the effect of histamine on acid secretion by decreasing the production of cyclic AMP. This may be the mechanism by which prostaglandin analogues inhibit acid secretion, as will be discussed later. Acetylcholine binds to a separate receptor, and its binding is blocked by atropine but not by $H_2$-receptor antagonists. Acetylcholine acts through a different intracellular messenger system and appears to increase the concentration of calcium in the cytoplasm of the parietal cell. Gastrin binds to a third receptor, and its binding is not blocked by either atropine or $H_2$-receptor antagonists. In experiments with animals, its effect can be blocked by certain weak gastrin-receptor antagonists, but none are potent enough to be useful clinically. Recent evidence suggests that gastrin, like acetylcholine, increases intracellular levels of calcium by accelerating the breakdown of certain phospholipids in the plasma membrane.

One point that I have emphasized is the different mechanism for transduction of these various external signals. This is of more than just academic importance, as these secretagogues have mutually potentiating effects. That is, the amount of acid produced by the parietal cell in response to stimulation by acetylcholine plus histamine, for example, is greater than the amount of acid that would be expected based on the summated responses of the parietal cell to acetylcholine or histamine alone. Although the mechanism of this potentiation has not yet been identified in parietal cells, it probably reflects interaction of these different second-messenger systems on one or more protein kinases that stimulate acid secretion.

From the clinical standpoint, this interaction is very important. It explains, for example, why blockade of the $H_2$ receptor with an $H_2$-receptor antagonist blocks the secretory response not only to histamine but to other secretagogues as well. It probably also explains why vagotomy, which presumably decreases stimulation of the acetylcholine receptor, blocks acid secretory response not only to stimulation of the vagus nerve and cholinergic stimuli, but also to other secretagogues as well. This has obvious clinical importance and relates directly to the mechanism of action of some of the agents to be discussed later.

### *The Mucosal Barrier*

The mucosal barrier is the denominator in the pseudo-equation proposed above, and it appears to be the site of the primary defect in patients with gastric ulcer disease and in patients with acute gastritis. As compared with the regulation of acid secretion, the function of the mucosal barrier is poorly understood.[7,9] It probably has multiple components, some of which are summarized in Table 1. Of these components, the production of mucus and bicarbonate by the surface epithelial cells has been most intensively studied and is perhaps best understood.[10-13] Mucus is a tenacious sub-

TABLE 1.—*Components of the Mucosal Barrier*

| |
|---|
| Secretion of mucus |
| Secretion of bicarbonate |
| Mucosal cell regeneration and restitution in response to injury |
| Mucosal blood flow |

stance that adheres to epithelial surfaces and is greater than 95% water by weight. The water that is trapped in this adherent layer mixes poorly with the bulk luminal contents of the stomach. The epithelial cells are also capable of secreting bicarbonate. While the rate of bicarbonate secretion is only about a tenth that of acid and therefore insufficient to neutralize bulk luminal acid, it does appear to be sufficient to neutralize acid that diffuses into this mucous layer from the lumen. The most convincing evidence for the existence of this mucus-bicarbonate barrier has come from studies using pH-sensitive microelectrodes.[11,12] When advanced micron by micron through this mucous layer, a steep pH gradient has been found in both animals and humans. The pH in the vicinity of the lumen is in the range of 1 to 2, and it is near neutral in the immediate vicinity of the surface mucosal cells. Agents such as prostaglandins, which accelerate the production of both mucus and bicarbonate, increase the pH in the immediate vicinity of the surface mucosal cells. Agents such as nonsteroidal anti-inflammatory drugs, which impair prostaglandin synthesis and secondarily impair the production of mucus and bicarbonate, impair the integrity of this mucus-bicarbonate layer and cause a breakdown of the pH gradient, such that the pH at the surface of the mucosal cells approaches that in the gastric lumen.

*Prostaglandins and mucosal defense.* Current concepts regarding the mucosal barrier have been derived largely from the study of the protective effect of prostaglandins on the gastric mucosa, and there is, in fact, moderately convincing evidence of a role for prostaglandins in the mucosal barrier, as follows.[14-19]

- Prostaglandins of the E and I type are produced by gastroduodenal mucosa, and their rate of production is increased by exposure to acid. This would be consistent with a physiologically regulated defense mechanism.
- Prostaglandins stimulate the secretion of mucus and bicarbonate, and the gastric ulcerogenic effects of nonsteroidal anti-inflammatory drugs may reflect their inhibitory effect on prostaglandin synthesis.
- Several studies suggest that gastric mucosal prostaglandin synthesis in ulcer patients is decreased as compared with controls.
- *Adaptive cytoprotection* is blocked by drugs that impair prostaglandin synthesis. Adaptive cytoprotection is a descriptive term that refers to the observation that exposure of the stomach to a low-level noxious stimulus enhances the ability of the stomach to withstand a subsequently greater ulcerogenic challenge. There is evidence that these noxious stimuli enhance prostaglandin synthesis, and adaptive cytoprotection—that is, the ability of the stomach to resist a subsequent ulcerogenic challenge—is blocked or at least attenuated by nonsteroidal anti-inflammatory drugs.
- Finally, certain slowly metabolizable prostaglandin analogues appear to protect against ulcer formation at doses that have no effect on acid secretion.

Collectively these observations suggest that prostaglandins may well be involved in the mucosal defense system.

*Other factors in mucosal defense.* While the evidence summarized above provides convincing support of a role for bicarbonate and mucus production by surface epithelial cells in mucosal defense, other mechanisms are clearly involved. Recent observations indicate that prostaglandins protect against gross gastric ulceration even under conditions in which the surface epithelial cells (and thus the mucus and bicarbonate barrier) are destroyed. The ability of surface epithelial cells to generate or migrate, or both, to cover injured areas appears to be important in mucosal defense; mucosal blood flow may also play a role.[19,20]

*Campylobacter and acid peptic disease.* One other interesting issue that merits mention in the context of the mucosal barrier is the recent reinvestigation of the possibility that certain acid peptic disorders have an infectious cause.[21] Several recent studies have found an apparent association between nonimmune gastritis and colonization or infection of the gastric mucosa with *Campylobacter pyloridis.* Collectively these studies indicate that this *Campylobacter* species can be recovered in the stomach of 60% to 90% of persons with histologically documented gastritis, whereas it is present in a much lower percentage of those without evidence of gastritis. *C pyloridis* has similarly been associated with discrete gastric and duodenal ulcers. This organism can be detected by special stains and, although it was initially identified by culture techniques used for other *Campylobacter* species, there remains some uncertainty regarding its appropriate classification.[21]

While these observations provide evidence of an association between mucosal injury and the presence of this organism, it is not clear whether the organism actually causes disease or whether it simply preferentially colonizes injured mucosa. Those investigators who propose a cause-and-effect relationship point out that ingesting the organism reportedly caused nonspecific symptoms and histologically documented gastritis in a single person and that the organism was subsequently identified in a biopsy of gastric mucosa.[22] An episode of apparently infectious gastritis reported from Dallas several years ago has also been subsequently linked to infection with *C pyloridis,*[23] although the evidence is not conclusive.

While the clinical implications of a cause-and-effect relationship between mucosal injury and infection by the *Campylobacter* species, which appears to be sensitive to a variety of antibiotics, are clearly important, most information bearing on this association has thus far been in the form of letters or abstracts, and much more data are required to clarify the nature of this relationship.

## Treatment of Acid Peptic Disorders

### *Current Issues in Management*

The development of cimetidine about ten years ago spawned a large number of controlled clinical trials in which the appearance or disappearance of ulcers was monitored endoscopically. Collectively these controlled trials have taught us a great deal about the natural history of acid peptic disease, and they have also brought into sharp focus certain problems in clinical management.

*Refractory ulcers.* The management of refractory ulcers is one such problem. Various therapies, to be discussed later, heal 70% to 90% of gastric or duodenal ulcers in six to ten

weeks, but 10% to 30% of ulcers are refractory to conventional forms of therapy. The best approach to patients with refractory ulcer disease is currently undetermined.[24-27]

*Recurrent ulcers.* A second issue that is perhaps even more important is that of ulcer recurrence. After healing, between 50% and 90% of duodenal ulcers relapse within a year, and most of these relapses occur in the first six months. It has also been shown that maintenance therapy with $H_2$-receptor antagonists or other agents can reduce this rate of relapse from around 8% to 9% per month to around 2% to 3% per month. These observations raise such questions as, is the likelihood of relapse predictable for a person, and is it related to the treatment that that patient received? Who should be given maintenance therapy? What agent should be used, and how long should it be administered?[28-34]

*Ulcer versus pain.* A third point relates to the disparity between ulcers and pain. While various agents have been shown to accelerate the disappearance of ulcer craters as compared with placebos, these agents have, in general, been less effective in accelerating the disappearance of symptoms.[35] Similarly, 50% of ulcers that recur following healing are not associated with symptoms. This dissociation between the presence of an ulcer and the presence of pain needs to be taken into account in developing a strategy for patients with ulcer disease.

*Smoking and ulcer disease.* The ulcer trials have also very clearly shown the adverse effect of smoking on peptic ulcer disease.[36-39] Smoking both retards the healing of ulcers and increases the likelihood of ulcer relapse. In England, about 80% of patients who undergo surgical treatment for acid peptic disease are smokers, and, in Scandinavia, where careful public health records are kept, about 90% of patients who have ulcer perforations are smokers. The deleterious effects of smoking on ulcer healing have been less apparent in trials involving the administration of agents that bolster the mucosal barrier, such as sucralfate, as compared with $H_2$-receptor antagonists or antacids.

*Effectiveness of current therapy.* Some investigators have raised the question of just what we accomplish with current medical therapy.[35] There are two reasons to treat patients with ulcers: one is to improve symptoms and the other is to prevent complications. As already mentioned, the various agents currently available are less effective in accelerating the disappearance of symptoms than in accelerating the disappearance of the ulcer crater.

Moreover, it has been very difficult to establish with certainty that administering any agent actually prevents ulcer complications such as perforation or hemorrhage (Table 2).[40] These observations suggest that currently available agents probably do not alter the natural history of peptic ulcer disease. Again, this is something that needs to be considered in clinical decision making.

TABLE 2.—*Complications of Duodenal Ulcer Disease—Incidence in 50 Placebo-Controlled Studies**†

| Patients | Placebo Number | Placebo (Percent) | Drugs Number | Drugs (Percent) |
|---|---|---|---|---|
| Entered study | 1,560 | (100.0) | 1,911 | (100.0) |
| Completed study | 1,419 | ( 91.0) | 1,767 | ( 92.5) |
| Dropped | 141 | ( 9.0) | 144 | ( 7.5) |
| Reasons for dropping | | | | |
| Unrelated to ulcer | 105 | ( 6.7) | 134 | ( 7.0)‡ |
| Related to ulcer | 36 | ( 2.3) | 11 | ( 0.5)‡ |
| Pain | 33 | ( 2.1) | 6 | ( 0.3) |
| Bleeding | 2 | ( 0.1) | 1 | ( 0.1) |
| Obstruction | 1 | ( 0.1) | 3 | ( 0.2) |
| Perforation | 0 | ( 0.0) | 0 | ( 0.0) |

*From Schiller and Fordtran.[40]

†The incidence of complications was determined by analysis of patients dropped from placebo or treatment groups during the course of the study. Note that of ulcer-related reasons for trial dropouts, worsening or intractable pain was the most frequent. Complications were infrequent and did not differ between groups.

‡$P < .05$.

## *Therapeutic Options for Acid Peptic Disease*

In reviewing the therapeutic options available for patients with duodenal or gastric ulcers, I would like to begin with an excerpt from a book by Boardman Reed, MD, of Temple University (Philadelphia) published in 1905.[41] As related to the treatment of round ulcer of the stomach, Dr Reed states that "it ought to be self-evident that for the healing of an ulcer, as well as for the repair of a broken bone, absolute bed rest is essential." Therefore, bed rest for four to six weeks was recommended, during which time patients were given nothing by mouth and fed only by enema. Physical therapy included hot abdominal compresses and abdominal massage, and medical therapy consisted of ice pellets for mild cases and sodium bicarbonate and bismuth for more severe cases.[41] Since the publication of Dr Reed's book, concepts regarding bed rest and diet certainly have changed, but ice-water lavage, antacids and bismuth preparations are still with us.

*Antacids.* There is a wide variety of antacid preparations available that differ in their content of sodium, magnesium and aluminum and in their potency, side effects and cost. Fortunately, there is currently a wide array of antacids to choose from that are high in potency and low in sodium content. Surprisingly, despite the fact that antacids have been used for decades, the optimal dose is not well established. The best-conducted studies showing efficacy of antacids for ulcer healing have used a high dose consisting of 140 mEq of a liquid antacid preparation given one and three hours after meals and at bedtime.[42-44] This intensive regimen is obviously inconvenient for patients, and recent studies suggest that lower doses may be effective. In fact, a single antacid tablet containing 120 mEq of acid-neutralizing capacity given four times a day has recently been shown to be effective in accelerating the healing of duodenal and gastric ulcers.[45,46] Although most authorities continue to recommend the high-dose antacid regimen, it is worth keeping in mind that the minimum effective dose of antacids is not well established.

It is also important to recall that antacids can diminish the absorption of other drugs, such as tetracycline, iron, digoxin, cimetidine and ranitidine. While this potential problem can be circumvented by staggering the administration of these agents rather than giving them simultaneously, the frequent dosing required for antacids does not allow much of a "therapeutic window."

*$H_2$-receptor antagonists.* $H_2$-receptor antagonists have emerged as the dominant form of therapy in the 1980s. Two preparations, cimetidine and ranitidine, have been available for several years,[47,48] and another high-potency $H_2$-receptor antagonist, famotidine, has been released recently.[49] Table 3 summarizes some of the points of comparison among these three agents.[50-59] Ranitidine and famotidine have a longer elimination half-life than cimetidine. In conjunction with a greater potency, this results in a longer duration of action for these agents as compared with cimetidine when given in

TABLE 3.—*$H_2$-Receptor Antagonists—Points for Comparison*

| *Indices* | *Cimetidine* | *Ranitidine* | *Famotidine* |
|---|---|---|---|
| Structure | Imidazole ring | Furan ring | Guanylthiazole ring |
| Elimination half-life, h | 2 | 3 | 4 |
| Relative potency | 1 | 5 to 14 | 20 to 160 |
| Duration of action, h (standard dose, mg) | 4 to 6 (300) | 8 to 12 (150) | 12 (20) |
| Inhibition of hepatic drug metabolism | Yes | Probably not | Probably not |
| Side effects | | | |
| Hypersensitivity | Rare | Rare | Rare* |
| CNS side effects | Rare | Rare | Rare* |
| Antiandrogenic effect | Dose related | No | No* |

CNS=central nervous system

*Limited postmarketing data.

"standard" doses. Recent studies indicate, however, that all three $H_2$-receptor antagonists are comparably effective in the healing of duodenal ulcers when given as a single night-time dose in large enough amounts. Thus, this difference in potency and duration of action may not be critical in the initial therapy for duodenal or gastric ulcer disease. It may be more relevant, however, for preventing ulcer relapse, as will be discussed below.

Cimetidine binds to hepatic cytochrome $P_{450}$ and inhibits the oxidative metabolism of a variety of drugs. This effect is probably most significant for theophylline, warfarin sodium and phenytoin, but even for these drugs, adverse clinical consequences have only rarely been reported. There is also preliminary evidence that a single night-time dose of cimetidine has less effect on the metabolism of these agents than does the multiple daily dosing regimen previously used. As compared with cimetidine, ranitidine binds weakly to hepatic cytochrome $P_{450}$. While minor effects of ranitidine ingestion on the metabolism of other drugs have been reported, they are probably not of clinical significance. Famotidine, like ranitidine, appears to have little effect on the metabolism of other drugs, but postmarketing clinical experience is limited.

Both cimetidine and ranitidine have proved to be remarkably safe agents. Hypersensitivity reactions and adverse effects on central nervous system function have been reported with both but are exceedingly rare. Recently there have been reports of an apparent association between the intravenous administration of ranitidine, particularly in doses of 100 mg or larger, and reversible abnormalities in liver function tests.[59] Famotidine, like cimetidine and ranitidine, appears to be associated with few side effects. Again, however, postmarketing experience with this agent is comparatively limited.

Antiandrogenic side effects including gynecomastia and impotence have been reported with the use of cimetidine, but not with the other agents. These are dose-related and are seen only in patients given large doses of the drug for a long period of time. Thus, for practical considerations, antiandrogenic side effects are a concern only for patients treated for the Zollinger-Ellison syndrome.

*Sucralfate.* Sucralfate is an aluminum salt of a sucrose octasulfate. The mechanism of action is not completely understood, but unlike the other agents discussed it appears to act by enhancing the mucosal barrier.[53,60-64] It appears to physically coat ulcers and may bind bile acids and pepsin; there is also evidence that it increases the mucosal synthesis of prostaglandins. Its use decreases the bioavailability of certain other drugs, and, as with animals, staggered administration is appropriate. Sucralfate has been shown to produce minimal side effects apart from constipation, which is dose-related. It appears to be effective for the treatment of duodenal ulcers and possibly also gastric ulcers, as well as for preventing ulcer recurrence.

*Bismuth preparations.* Bismuth-containing preparations, currently available in Europe but not in the United States, have also been effective in healing ulcers.[30,31] The mechanism of action of such agents is unknown, but because bismuth is not known to neutralize acid or inhibit secretion, it is presumed to act by enhancing the mucosal barrier. Of interest is that two studies have shown that duodenal ulcers healed with a bismuth preparation are less likely to relapse than ulcers healed with an $H_2$-receptor antagonist (see below). I am not aware of similar studies looking at nonprescription bismuth preparations available in the United States.

*Omeprazole.* Omeprazole is the newest and most potent agent in terms of its ability to inhibit acid secretion.[65-70] It inhibits the $H^+$, $K^+$-ATPase that mediates the final step in acid secretion. Its potency is much greater than that of $H_2$-receptor antagonists, and it has a longer duration of action. A single dose can decrease acid output by more than 90% for a period of 24 hours or more. It accumulates and is concentrated in the highly acidic compartments of the parietal cell. When activated by acid, omeprazole attacks sulfhydryl groups and irreversibly inactivates the $H^+$, $K^+$-ATPase, which helps to explain its long duration of action. The accumulation of omeprazole in parietal cells also explains a peculiar pharmacokinetic property of this drug: namely, it is maximally effective at a time when drug concentrations in the blood are no longer detectable.

Omeprazole has been effective for the treatment of duodenal ulcer disease, and its high potency and long duration of action are particularly attractive for the treatment of the Zollinger-Ellison syndrome,[69,70] which is associated with a dramatic hypersecretion of acid.

Recently it was noted that administering omeprazole to rats produced gastric carcinoid tumors, causing concern that the drug was intrinsically carcinogenic. Recent evidence, however, suggests that this is not the case.[71] Carcinoid tumors have also been associated with the administration of high-potency $H_2$-receptor antagonists[72] and are described in association with pernicious anemia. Thus, carcinoid tumors appear not to be due to omeprazole per se but rather to the profound inhibition of acid secretion and accompanying hypergastrinemia that the drug produces. Gastrin, in turn, appears to stimulate certain endocrine-like cells in the gastric mucosa, which may lead to the production of carcinoid tumors.

*Prostaglandin analogues.* Prostaglandin analogues are being intensively investigated by several different pharmaceutical houses.[73-75] They have an appealing therapeutic rationale in that they inhibit gastric acid secretion and also appear to bolster the mucosal barrier, perhaps in part by increased production of mucus and bicarbonate. The duration of action of these analogues is relatively short, and dosing several times per day is likely to be necessary. Premarketing trials suggest that prostaglandin analogues are comparable in efficacy to the $H_2$-receptor antagonist for the initial short-term treatment of duodenal and gastric ulcers. There is as yet little information bearing on longer periods of administration or the use of these analogues for maintenance treatment. Dose-related diarrhea has been the main side effect.

*Anticholinergics.* Anticholinergic agents are infrequently used in the United States because of their side effects. Certain anticholinergic and tricyclic antimuscarinic agents are reportedly more selective in their effects and are widely used in Western Europe and Scandinavia.[76] These may be available in the United States in the relatively near future.

*Combined drug therapy.* There is, in general, little evidence that the combined administration of these drugs accomplishes more than administering individual agents. The only combination that has been clearly shown to be effective is combining an $H_2$-receptor antagonist with an anticholinergic. This makes good therapeutic sense and has been used in patients with the Zollinger-Ellison syndrome. There is no convincing evidence, however, that the combined administration of antacids and an $H_2$-receptor antagonist offers anything over the administration of either one alone. The picture with respect to the combined administration of sucralfate and an $H_2$-receptor antagonist is unclear. A currently ongoing study suggests that giving the two agents together may offer some marginal advantage over administering either agent alone in that ulcer healing is more rapid at two weeks.[63] At six to eight weeks there appears to be no difference between the results of these agents given alone or in combination. I am not aware of any data on the combined administration of either prostaglandin analogue or omeprazole with other agents.

### *Treatment of Specific Disorders*

*Duodenal ulcer disease.* Having reviewed the therapeutic options, it is reasonable to consider the therapeutic approach to specific acid peptic disorders. Various forms of therapy, summarized in Table 4, have been shown to accelerate the disappearance of a duodenal ulcer crater as compared with placebo. The considerations that arise in choosing among these agents include efficacy, safety, cost and convenience. With respect to efficacy, there is not a great deal to choose among the various agents. The standout performer in the few available studies thus far published has been omeprazole, which produces a healing rate of 95% in just four weeks. The relatively large doses of omeprazole used in these studies, however, might produce hypergastrinemia, and the safety of omeprazole given in these doses is not established. Moreover, omeprazole is not yet released for general use.

The remaining agents are all remarkably safe, and safety is therefore also not a distinguishing factor. If not efficacy or safety, is cost a distinguishing factor? The cost of antacids varies considerably depending on the brand chosen and place of purchase. Generally, however, the cost of a high-potency antacid regimen is somewhat greater than that of ranitidine, which is slightly greater than the cost of cimetidine, which is comparable to that of sucralfate. Thus, cost would not necessarily be a deciding factor for an individual patient. Given the frequency with which these agents are prescribed, however, small differences in cost have a potentially important impact on health care costs at the national level.

TABLE 4.—*Duodenal Ulcer Treatment of Established Efficacy**

| *Agents* | *Dose* |
|---|---|
| Antacids | 70/140 mEq (liquid) 1 to 3 h after meals and at bedtime; *or* 120 mEq tablet, 1 qid |
| $H_2$-Receptor antagonists | |
| Cimetidine | 300 mg qid, *or* 400 mg bid, *or* 800 mg at bedtime |
| Ranitidine | 150 mg bid, *or* 300 mg at bedtime |
| Famotidine | 20 mg bid, *or* 40 mg bid, *or* 40 mg at bedtime |
| Sucralfate | 1 gram qid, *or* 2 grams bid |
| Omeprazole | 30 to 60 mg a day |

bid=twice a day, qid=4 times a day

*Includes only agents currently available in the United States.

In contrast to efficacy, safety and cost, convenience is an important distinguishing factor, and a single night-time dose of an $H_2$-receptor antagonist currently appears to have the edge. This convenient regimen appears to be just as effective, and possibly more effective, in healing duodenal ulcers than the previously used multiple-dosing regimen. Increased convenience presumably results in increased patient compliance and possibly an overall increase in efficacy. Deciding among the three $H_2$-receptor antagonists depends on factors already discussed. For the vast majority of persons with uncomplicated acid peptic ulcer disease, the three agents are probably equivalent.

Sucralfate offers an attractive option for a patient in whom one would like to avoid a systemically acting agent, such as a young woman who is likely to become pregnant. There is also some evidence that the deleterious effects of smoking on ulcer healing are less apparent with sucralfate than with the $H_2$-receptor antagonists. Sucralfate may also merit special consideration for a smoker with acid peptic disease.

Having selected an agent, a reasonable strategy is to treat the patient with a duodenal ulcer for a period of six to eight weeks and stop. If symptoms disappear and do not recur, then no further investigation or treatment is advisable. This approach acknowledges the fact that half or more of such patients successfully treated will have a recurrence of their ulcer and that many of these recurrences will be asymptomatic. This approach thus involves the tacit and probably reasonable assumption that the vast majority of these asymptomatic recurrences will not lead to complications.

Finally, there is a modest body of evidence that recurrence of duodenal ulcers occurs less rapidly after treatment with agents that appear to act by enhancing the mucosal barrier—that is, bismuth preparations and possibly sucralfate—than after treatment with antacids or $H_2$-receptor antagonists (Table 5).[30-34] Should future studies support these preliminary observations, they may have an important bearing on selection of the initial therapy.

*Gastric ulcer disease.* As compared with duodenal ulcer, gastric ulcers tend to be slower to heal, and the effects of various agents, summarized in Table 6, on gastric ulcer healing as compared with placebo have been less dramatic. This in part reflects the rather rapid healing rate of gastric ulcers on placebo therapy, which is often 50% to 70% at 8 to

TABLE 5.—*Ulcer Relapse Rate and Effect of Initial Treatment**

| Study | Patients, number | Comparison | Follow-up, mos | Results |
|---|---|---|---|---|
| Martin et al, 1981[30] | 75 | Cimetidine *v* bismuth | 12 | 86% *v* 40%† |
| Hamilton et al, 1985[31] | 80 | Cimetidine *v* bismuth | 12 | 78% *v* 43%† |
| Ippoliti et al, 1983[32] | 114 | Cimetidine *v* antacids | 6 | 55% *v* 56% |
| Marks et al, 1983[33] | 86 | Cimetidine *v* sucralfate | 6 | 69% *v* 70%‡ |
| Strom et al, 1981[34] | 72 | Cimetidine *v* antacids plus an anticholinergic *v* placebo | 12 | 73% *v* 50% *v* 56%§ |

*Summary of several trials involving different treatment regimens and varying periods of follow-up of patients with predominantly duodenal ulcer disease
†$P < .05$
‡Relapses occurred sooner (4.6 versus 7.3 months) with cimetidine.
§Symptomatic relapse only; relapses occurred sooner with cimetidine.

TABLE 6.—*Gastric Ulcer Treatment of Established Efficacy**

| Agent | Dose |
|---|---|
| Antacids | 70/140 mEq (liquid) 1 to 3 h after meals and at bedtime |
| $H_2$-Receptor antagonists | |
| Cimetidine | 300 mg qid, *or* 800 mg at bedtime |
| Famotidine | 20 mg bid, *or* 40 mg at bedtime |
| Ranitidine | 150 mg bid, *or* 300 mg at bedtime |
| Sucralfate | 1 gram qid |

bid=twice a day, qid=4 times a day

*Includes only agents currently avaliable in the United States.

12 weeks. The considerations that arise in choosing among the treatment options are basically the same as those discussed above with respect to the treatment of duodenal ulcer disease. Convenience, again, is an important factor, and again a single night-time dose of an $H_2$-receptor antagonist is most convenient. There is, however, less information bearing on this regimen for gastric ulcers than there is for duodenal ulcers.

Sucralfate has been less thoroughly studied for the treatment of gastric ulcers as compared with duodenal ulcers, and there is less convincing evidence of its efficacy for gastric ulcer disease than for duodenal ulcer disease. As with duodenal ulcer disease, sucralfate can represent an attractive alternative under special circumstances.

Apart from choosing a specific agent, the special consideration that arises in patients with gastric ulcer disease is the concern regarding malignancy, and it is generally appropriate to endoscope all patients with a radiologically diagnosed gastric ulcer. It is noteworthy in this regard that a recent large study found that about 5% of radiologically benign gastric ulcers were, in fact, malignant.[51] Moreover, a third of these malignant lesions were identified only at the second endoscopic session. Therefore, it is appropriate to follow up on gastric ulcers to complete healing. If there is radiologic or endoscopic evidence of nonhealing in 12 weeks, a repeat biopsy is appropriate.

*Refractory ulcers.* As summarized above, various agents heal 70% to 90% of duodenal or gastric ulcers in a period of 6 to 12 weeks, but there remains a hard-core 10% to 30% of ulcers that do not heal in this period.[24-27] Given such a patient with a nonhealing ulcer, a first step would be to assess risk factors and patient compliance. Is this patient, for example, a smoker who might be expected to have a slower healing rate, and is the patient compliant with the prescribed treatment? If patient compliance is not an issue, it is reasonable to consider a hypersecretory state, the possibility of cancer (particularly in a patient with gastric ulcer) or other disorders such as Crohn's disease, tuberculosis or lymphoma that can occasionally mimic peptic ulcer disease.

Assuming that one is dealing with benign but refractory peptic ulcer disease, the treatment strategies include pressing ahead with the same form of therapy, altering medical therapy or surgical intervention. The data on which to make a judgment are limited, but the available evidence suggests that it is better to change therapy than to continue with the same agent. In one study, 80% of ulcers that failed to heal on cimetidine therapy did heal when the patients were switched to a bismuth preparation.[25] By comparison, only 40% of comparable patients who were treated for an additional several months with an increased dose of cimetidine experienced healing.[25] The reverse might well be true for ulcers that are refractory to healing on a regimen of bismuth preparations or sucralfate. Obviously, surgical treatment remains an option for patients with refractory disease.

### *Ulcer Recurrence*

It is becoming increasingly apparent that it is not as difficult to get an ulcer healed as it is to keep it healed.[77-81] A variety of risk factors have emerged from various studies as important predictors of ulcer recurrence. The most important risk factor appears to be smoking—as discussed earlier. Other risk factors identified in some studies include male sex, a long prior history of ulcer disease, a history of previous recurrences, a family history of disease or pronounced acid hypersecretion.

In general, the indications for maintenance therapy for acid peptic disease parallel directly the severity and the frequency of ulcer recurrence. Indications for maintenance therapy would include poor operative candidacy, frequent or severe symptomatic recurrences and, in particular, a history of previous complications such as bleeding. Obviously patients with the Zollinger-Ellison syndrome in whom the gastrinoma cannot be resected are also candidates for maintenance therapy.

Surgical treatment is also an option for patients with symptomatic recurrent or complicated ulcer disease. Because it is becoming increasingly clear that currently available agents probably do not alter the natural history of ulcer disease, a surgical procedure deserves careful consideration for otherwise healthy patients who are operative candidates. Even if continuous treatment with an $H_2$-receptor antagonist reduced the rate of ulcer recurrence to 15% per year, then 50% or more of patients would be expected to have a relapse over a five-year period. Table 7 summarizes the various forms

TABLE 7.—*Treatment of Established Efficacy in Preventing Ulcer Relapse*

| *Agent* | *Dose* |
|---|---|
| $H_2$-Receptor antagonists | |
| Cimetidine | 400 mg at bedtime, *or* 400 mg bid |
| Ranitidine | 150 mg at bedtime |
| Famotidine | 20 mg at bedtime* |
| Sucralfate | 1 gram bid |

bid=twice a day

*Limited data.

of therapy that have been effective in preventing ulcer relapse. While the $H_2$-receptor antagonists have been most intensively studied and are clearly effective in reducing the rate of ulcer relapse, sucralfate has also been shown to be effective in several studies and represents an attractive agent in certain circumstances.

Several studies have now directly compared the effectiveness of cimetidine and ranitidine. While most studies have not indicated a difference between the two agents, two recent studies have.[80,81] One from Europe and Australia compared the effectiveness of 150 mg of ranitidine with 400 mg of cimetidine, both given as a single dose at bedtime, and at 4 months, 8 months and 12 months, the apparent incidence of ulcer relapse was greater for cimetidine than for ranitidine.[81] A second study conducted in the United States with a similar design yielded similar results.[80] Given the difference in potency of these two agents and their duration of action (Table 3), these findings are not surprising, and one might anticipate that a larger night-time dose of cimetidine would be equivalent to the use of ranitidine. This has not yet been established, however.

*Nonulcer Dyspepsia*

The entire discussion up to this point has focused on patients with an endoscopically or radiographically documented duodenal or gastric ulcer. What about a patient who has ulcerlike symptoms, but does not have a radiographically or endoscopically identifiable ulcer crater? The number of such patients, in fact, is probably at least as great as the number of patients who have a documented ulcer.[82–85] Several recent studies have addressed the efficacy of therapy for these patients, and the results of the various studies have differed. One large recent study compared, in a double-blind manner, the effects of placebo, antacids and cimetidine over a period of three weeks.[84] Two points emerged. First, there was no difference among these agents in accelerating the disappearance of symptoms. Second, regardless of whether the patients received an active agent or a placebo, there was a striking trend toward improvement during the course of the study. In fact, this latter observation is a common one among cyclical chronic disorders because patients tend to present when their symptoms are severe, and gradual improvement with time is common regardless of treatment.

In contrast to these results, other studies suggest that $H_2$-receptor antagonists or antacids are, in fact, significantly (albeit sometimes only slightly) superior to placebo in resolving symptoms in patients with nonulcer dyspepsia.[82,83,85] How are these differing results to be explained? In fact, the differing results of these studies probably reflect the nature of the disease being studied as well as the selection of patients. Because even in patients with verified ulcer active agents have a less impressive effect on the disappearance of symptoms than on the disappearance of the ulcer crater, it is unreasonable to expect a dramatic effect of treatment on symptoms in patients with nonulcer dyspepsia. Second, those studies that have rigorously excluded patients with a history of duodenal ulcer disease or with evidence of gastritis or duodenitis on endoscopy have tended to show less of an effect of treatment than the trials that have not excluded such patients. Thus, the more "ulcerlike" a patient in terms of evidence of mucosal injury or a positive past history, the greater the apparent benefit of treatment. Given a patient with ulcerlike symptoms and a history of ulcer disease or some objective evidence of inflammation on endoscopy, an empiric trial of antacids or an $H_2$-receptor antagonist would be reasonable. In the absence of objective evidence of disease or a positive history, the merits of therapy are less clear. In fact, such a patient may have the irritable bowl syndrome, which responds poorly to any agent and is really the subject of an entirely different lecture.

## Questions and Answers

PHYSICIAN IN THE AUDIENCE: *Are calcium channel blockers effective in reducing acid secretion?*

DR SCHARSCHMIDT: This question relates to the fact that calcium is involved in the transduction of some extracellular signals. Calcium channel blockers appear to have an effect, but it is a weak one. This may reflect the fact that much of the increase in cytosolic calcium produced by gastrin and possibly acetylcholine represents release from intracellular stores as opposed to enhanced calcium flux across the plasma membrane.

PHYSICIAN IN THE AUDIENCE: *I noticed that you did not say anything about the role of diet in the treatment of these patients. What is the role of a bland diet, avoiding caffeine and peppery food and so on?*

DR SCHARSCHMIDT: There is very little, if any, documented role for strict adherence to a particular diet. Currently we recommend that patients eat three regular meals a day and avoid snacking between meals. Most clinicians also suggest that the patients minimize or eliminate the ingestion of coffee and alcohol, but there are few data to support that recommendation.

PHYSICIAN IN THE AUDIENCE: *Do corticosteroids cause ulcers and should patients taking corticosteroids be given antacids or another antiulcer agent?*

DR SCHARSCHMIDT: It is amazing how much controversy that question has generated. It is particularly surprising because the two best-known studies that have emerged with opposite conclusions did so based on similar findings.[86–88] Both the study by Conn and Blitzer[86] and that by Chalmers and colleagues[87] suggest that corticosteroids produce about a twofold increase in the risk of an ulcer developing. My own feeling is that the routine administration of another agent, such as antacids or an $H_2$-receptor antagonist, is not warranted for patients receiving corticosteroids alone. If there is already evidence of acid peptic disease or if the patient is receiving another drug like a nonsteroidal anti-inflammatory agent, then the issue is less clear.

PHYSICIAN IN THE AUDIENCE: *Does chloroquine affect the ability of the parietal cell to be stimulated?*

DR SCHARSCHMIDT: This is an interesting question in the sense that chloroquine is a weak base that is accumulated in acidic compartments and increases their internal pH. In the doses used clinically, I am unaware of any effect of chloroquine on acid secretion. In in vitro systems, chloroquine does not appear to affect stimulus-secretion coupling.

#### REFERENCES


1. Richardson CT: Pharmacologic basis of peptic ulcer therapy. Viewpoints Dig Dis 1985; 17:1-4

2. Olson C, Soll AH: The parietal cell and regulation of gastric acid secretion. Viewpoints Dig Dis 1984; 16:1-4

3. Forte JG, Black JA, Forte TM, et al: Ultrastructural changes related to functional activity in gastric oxyntic cells. Am J Physiol 1981; 241:G349-G358

4. Hirst BH, Forte JG: Redistribution and characterization of ($H^+$-$K^+$)-ATPase membranes from resting and stimulated gastric parietal cells. Biochem J 1985; 231:641-649

5. Cuppoletti J, Sachs G: Regulation of gastric acid secretion via modulation of a chloride conductance. J Biol Chem 1984; 259:14952-14959

6. Wallmark B, Larsson H, Humble L: The relationship between gastric acid secretion and gastric $H^+$, $K^+$-ATPase activity. J Biol Chem 1985; 260:13681-13684

7. Flemström G, Turnberg LA: Gastroduodenal defense mechanisms. Clin Gastroenterol 1984; 13:327-354

8. Guth PH: Pathogenesis of gastric mucosal injury. Annu Rev Med 1982; 33:183-196

9. Rees WDW, Turnberg LA: Mechanisms of gastric mucosal protection: A role for the 'mucus-bicarbonate' barrier. Clin Sci 1982; 62:343-348

10. Allen A, Garner A: Mucus and bicarbonate secretion in the stomach and their possible role in mucosal protection. Gut 1980; 21:249-252

11. Ross IA, Bahari HMM, Turnberg LA: The pH gradient across mucus adherent to rat fundic mucosa in vivo and the effect of potentially damaging agents. Gastroenterology 1981; 81:713-718

12. Williams SE, Turnberg LA: Studies of the protective properties of gastric mucus. Adv Exp Med Biol 1982; 144:184-188

13. LaMont JT: Structure and function of gastrointestinal mucus. Viewpoints Dig Dis 1985; 17:1-4

14. Konturek SJ, Brzozowski T, Piastucki I, et al: Role of locally generated prostaglandins in adaptive gastric cytoprotection. Dig Dis Sci 1982; 27:967-971

15. Sharon P, Cohen F, Zefroni A, et al: Prostanoid synthesis by cultured gastric and duodenal mucosa: Possible role in the pathogenesis of duodenal ulcer. Scand J Gastroenterol 1983; 18:1045-1049

16. Ahlquist DA, Dozois RR, Zinsmeister AR, et al: Duodenal prostaglandin synthesis and acid load in health and in duodenal ulcer disease. Gastroenterology 1983; 85:522-528

17. Robert A, Nezamis JE, Lancaster C, et al: Mild irritants prevent gastric necrosis through 'adaptive cytoprotection' mediated by prostaglandins. Am J Physiol 1983; 245:G113-G121

18. Chailet N, Gallo-Torres HE, Bounameaux Y, et al: Prostaglandins and the protection of the gastroduodenal mucosa in humans: A critical review. J Clin Pharmacol 1985; 25:564-582

19. Leung FW, Robert A, Guth PH: Gastric mucosal blood flow in rats after administration of 16,16-dimethyl prostaglandin $E_2$ at a cytoprotective dose. Gastroenterology 1985; 88:1948-1953

20. Lacy ER: Prostaglandins and histological changes in the gastric mucosa. Dig Dis Sci 1985; 30:835-945

21. Rathbone BJ, Wyatt JI, Heatley RV: Campylobacter pyloridis—A new factor in peptic ulcer disease. Gut 1986; 27:635-641

22. Marshall BJ, Armstrong JA, McGechie DB, et al: Attempt to fulfill Koch's postulates for pyloric *Campylobacter*. Med J Aust 1985; 142:436-439

23. Ramsey EJ, Carey KV, Peterson WL, et al: Epidemic gastritis with hypochlorhydria. Gastroenterology 1979; 76:1449-1457

24. Bardham KD: Refractory duodenal ulcer. Gut 1984; 25:711-717

25. Lam SK, Lee NW, Koo J, et al: Randomised crossover trial of tripotassium dicitrato bismuthate versus high dose cimetidine for duodenal ulcers resistant to standard doses of cimetidine. Gut 1984; 25:703-706

26. Quatrini M, Basilisco G, Bianchi PA: Treatment of 'cimetidine-resistant' chronic duodenal ulcers with ranitidine or cimetidine: A randomised multicentre study. Gut 1984; 25:1113-1117

27. Pounder RE: Duodenal ulcers that will not heal. Gut 1984; 25:697-702

28. Wormsley KG: Assessing the safety of drugs for the long-term treatment of peptic ulcers. Gut 1984; 25:1416-1423

29. Sonnenberg A, Webersinke R: The costs of medical and surgical treatment of duodenal ulcer disease (Abstr). Gastroenterology 1986; 90:1643

30. Martin DF, Hollanders D, May SJ, et al: Difference in relapse rates of duodenal ulcer after healing with cimetidine or tripotassium dicitrato bismuthate. Lancet 1981; 1:7-10

31. Hamilton I, O'Connor HJ, Wood NC, et al: Healing and recurrence of duodenal ulcer after treatment with tripotassium dicitrato bismuthate tablets (TDB) or cimetidine. Gut 1985; 27:106-110

32. Ippoliti A, Elashoff J, Valenzuela J, et al: Recurrent ulcer after successful treatment with cimetidine or antacid. Gastroenterology 1983; 85:875-880

33. Marks IN, Wright JP, Lucke W, et al: Relapse rates following initial ulcer healing with sucralfate and cimetidine. Scand J Gastroenterol 1983; 18(suppl 83):53-56

34. Strom M, Gotthard R, Bodeman G, et al: Antacid/anticholinergic, cimetidine and placebo in treatment of active peptic ulcers. Scand J Gastroenterol 1981; 16:593-602

35. Goldberg MA: Medical treatment of peptic ulcer disease: Is it truly effective? Am J Med 1984; 77:589-591

36. Korman MG, Shaw RG, Hansky J, et al: Influence of smoking on healing rate of duodenal ulcer in response to cimetidine or high dose antacid. Gastroenterology 1981; 80:1451-1453

37. Boyd EJS, Wilson JA, Wormsley KG: Smoking impairs therapeutic gastric inhibition. Lancet 1983; 1:95-97

38. Sontag S, Graham DY, Belsito A, et al: Cimetidine, cigarette smoking, and recurrence of duodenal ulcer. N Engl J Med 1984; 311:689-693

39. McCarthy DM: Smoking and ulcers—Time to quit. N Engl J Med 1984; 311:726-728

40. Schiller LR, Fordtran JS: Ulcer complications during short term therapy of duodenal ulcer with active agents and placebo. Gastroenterology 1985; 90:478-479

41. Reed B: Diseases of the Stomach and Intestine. Bristol, England, John Wright, 1905

42. Peterson WL, Sturdevant RAL, Frankl HD, et al: Healing of duodenal ulcer with an antacid regimen. N Engl J Med 1977; 297:341-345

43. Fordtran JS, Morawski SG, Richardson CT: In vivo and in vitro evaluation of liquid antacids. N Engl J Med 1973; 288:923-928

44. Lauritsen K: Comparison of ranitidine and high dose antacid in the treatment of prepyloric or duodenal ulcer. Scand J Gastroenterol 1985; 20:123-131

45. Weberg R: Duodenal ulcer healing with four antacid tablets daily. Scand J Gastroenterol 1985; 20:1041-1045

46. Rydning A, Weberg R, Lange O, et al: Healing of benign gastric ulcer with low dose antacids and fiber diet. Gastroenterology 1986; 91:56-61

47. Freston JW: Cimetidine—I. Development, pharmacology, and efficacy; II. Adverse reactions and patterns of use. Ann Intern Med 1982; 97:573-580; 728-734

48. Zeldis JB, Friedman LS, Isselbacher KJ: Ranitidine: A new $H_2$-receptor antagonist. N Engl J Med 1983; 309:1368-1373

49. Smith JL: Clinical pharmacology of famotidine. Digestion 1985; 32:15-23

50. Graham DY, Akdamar K, Dyck WP, et al: Healing of benign gastric ulcer: Comparison of cimetidine and placebo in the United States. Ann Intern Med 1985; 102:573-576

51. Isenberg JI, Peterson WL, Elashoff JD, et al: Healing of benign gastric ulcer with low dose antacid or cimetidine—A double blind, randomized placebo-controlled trial. N Engl J Med 1983; 308:1319-1324

52. Legerton CW: Duodenal and gastric ulcer healing rates: A review. Am J Med 1984; 77:2-7

53. Hallerback B, Aanker-Hansen O, Carling L, et al: Short term treatment of gastric ulcer: A comparison of sucralfate and cimetidine. Gut 1986; 27:778-783

54. Gitlin N, McCullough AJ, Smith JL: A multicenter, double-blind, randomized, placebo-controlled comparison of nocturnal and twice-a-day famotidine in the treatment of active duodenal ulcer disease. Gastroenterology 1987; 92:48-53

55. Ireland A, Colin-Jones DG, Gear P, et al: Ranitidine 150 mg twice daily vs 300 mg nightly in treatment of duodenal ulcers. Lancet 1984; 2:274-276

56. Kildebo S, Aronsen O, Bernersen B, et al: Cimetidine, 800 mg at night, in the treatment of duodenal ulcers. Scand J Gastroenterol 1985; 20:1147-1150

57. Lee FI, Reed PI, Crowe JP, et al: Acute treatment of duodenal ulcer: A multicentre study to compare ranitidine 150 mg twice daily with ranitidine 300 mg once at night. Gut 1986; 27:1091-1095

58. Ryan FP, Jorde R, Ehsanullah RSB, et al: A single night time dose of ranitidine in the acute treatment of gastric ulcer: A European multicentre trial. Gut 1986; 27:784-788

59. Souza-Lima MA: Ranitidine and hepatic injury. Ann Intern Med 1986; 105:140

60. Richardson CT: Sucralfate (Editorial). Ann Intern Med 1982; 97:269-272

61. Miyake T, Ariyoshi J, Suzaki T, et al: Endoscopic evaluation of the effect of sucralfate therapy and other clinical parameters on the recurrence rate of gastric ulcers. Dig Dis Sci 1980; 25:1-7

62. Martin F, Farley A, Gagnon M, et al: Comparison of the healing capacities of sucralfate and cimetidine in the short-term treatment of duodenal ulcer: A double blind randomized trial. Gastroenterology 1982; 82:401-405

63. Van Deventer G, Schneidman D, Walsh JH: Sucralfate and cimetidine as single agents and in combination for treatment of active duodenal ulcers: A double-blind, placebo-controlled trial. Am J Med 1985; 79(2c):39-44

64. Brandstaetter G, Kratochvil P: Comparison of two sucralfate dosages (2 g twice a day versus 1 g four times a day) in duodenal ulcer healing. Am J Med 1985; 79(2c):36-38

65. Londong W, Londong V, Cederberg C, et al: Dose-response study of omeprazole on meal-stimulated gastric acid secretion and gastrin release. Gastroenterology 1983; 85:1373-1378

66. Gustavsson S, Adami HO, Lööf L, et al: Rapid healing of duodenal ulcers with omeprazole: Double-blind dose-comparative trial. Lancet 1983; 2:124-125

67. Lauritsen K, Rune SJ, Bytzer P, et al: Effect of omeprazole and cimetidine on duodenal ulcer. N Engl J Med 1985; 312:958-961

68. Nielsen AM, Stenderup J, Wandall JH, et al: Reduction of gastric acid secretion by 10 mg and 30 mg omeprazole once daily. Scand J Gastroenterol 1985; 20:1236-1238

69. Lamers CBHW, Lind T, Moberg S, et al: Omeprazole in Zollinger-Ellison syndrome. N Engl J Med 1984; 310:758-761

70. McArthur KE, Collen MJ, Maton PH, et al: Omeprazole: Effective, convenient therapy for Zollinger-Ellison syndrome. Gastroenterology 1985; 88:939-944

71. Elder JB: Inhibition of acid and gastric carcinoids. Gut 1985; 26:1279-1283

72. Poynter D, Pick CR, Harcourt RA, et al: Association of long lasting insurmountable histamine $H_2$ blockade and gastric tumors in the rat. Gut 1985; 26:1284-1295

73. Vantrappen G, Janssens J, Popiela T: Effect of 15,15-dimethyl prostaglandin $E_2$ on the healing of duodenal ulcer. Gastroenterology 1982; 83:357-363

74. Fick A, Arber N, Sestieri M, et al: Effect of misoprostel and cimetidine on gastric cell labelling index. Gastroenterology 1985; 89:57-61

75. Brooks FP, Watkinson G, Davies HC (Eds): Prostaglandins in gastroenterology—Focus on misoprostel. Dig Dis Sci 1985; 30:1S-205S

76. Adami HO, Bjorklund O, Enandes L-K, et al: Cimetidine or propantheline combined with antacid therapy for short-term treatment of duodenal ulcer. Dig Dis Sci 1982; 27:388-393

77. Van Deventer GM: Approaches to the long-term treatment of duodenal ulcer disease. Am J Med 1984; 77:15-22

78. Robinson M: Review of the peptic ulcer maintenance trials. Am J Med 1984; 77:23-29

79. Marks IN, Wright JP, Girdwood AH, et al: Maintenance therapy with sucralfate reduces rate of gastric ulcer recurrence. Am J Med 1985; 79(2c):14-17

80. Silves SE: Final report on the United States multicenter trial comparing ranitidine to cimetidine as a maintenance therapy following healing of duodenal ulcer. J Clin Gastroenterol 1985; 7:482-487

81. Gough KR, Korman MG, Bardhan KD, et al: Ranitidine and cimetidine in prevention of duodenal ulcer relapse—A double blind, randomised, multicentre comparative trial. Lancet 1984; 2:659-662

82. Kleveland PM, Larsen S, Sandvick L, et al: The effect of cimetidine on nonulcer dyspepsia. Scand J Gastroenterol 1985; 20:19-24

83. Nesland AA, Berstad A: Effect of cimetidine in patients with non-ulcer dyspepsia and erosive prepyloric changes. Scand J Gastroenterol 1985; 20:629-635

84. Nyren O, Adami HO, Bates S, et al: Absence of therapeutic benefit from antacids or cimetidine in non-ulcer dyspepsia. N Engl J Med 1986; 314:339-343

85. Talley NJ, McNeil D, Hayden A, et al: Randomized double-blind, placebo-controlled crossover trial of cimetidine and pirenzipine in nonulcer dyspepsia. Gastroenterology 1986; 91:149-156

86. Conn HO, Blitzer BL: Nonassociation of adrenocorticosteroid therapy and peptic ulcer. N Engl J Med 1976; 294:473-479

87. Messer J, Reitman D, Sacks HS, et al: Association of adrenocorticosteroid therapy and peptic-ulcer disease. N Engl J Med 1983; 309:21-24

88. Spiro HM: Is the steroid ulcer a myth? N Engl J Med 1983; 309:45-47

Epitomes
Important Advances in Clinical Medicine

# General Surgery

*The Scientific Board of the California Medical Association presents the following inventory of items of progress in general surgery. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, research workers or scholars to stay abreast of these items of progress in general surgery that have recently achieved a substantial degree of authoritative acceptance, whether in their own field of special interest or another.*

*The items of progress listed below were selected by the Advisory Panel to the Section on General Surgery of the California Medical Association and the summaries were prepared under its direction.*

Reprint requests to Division of Scientific and Educational Activities, California Medical Association, PO Box 7690, San Francisco, CA 94120-7690

## New Advances in Pancreatic Transplantation

TRANSPLANTATION OF THE PANCREAS is an effective means of achieving an insulin-independent, euglycemic state in patients with type I diabetes mellitus and, thus, possibly preventing the late renal, vascular and cardiac complications.

Pancreas allotransplantation is being done with increasing frequency and greater success rates. About 1,000 cases have been reported to date, with more than 400 transplants carried out during the period 1983 through 1985, having a one-year success rate of 44%. Over the past two years, with improvements in surgical technique, one-year graft survival rates of 60% to 75% have been reported. With increasing experience, pancreas transplantation has become a safer procedure. At most major centers in the country, the one-year mortality rate for this operation (about 10%) matches that of renal transplants carried out in diabetic patients. While long-term graft survival results are not available, the longest functioning pancreatic allograft reported is eight years.

Various surgical techniques have been used, including transplantation of the entire gland (with or without the duodenum) or of the body and tail (segmental). The "Achilles heel" of the procedure has been management of the exocrine secretions. A diverse number of techniques has been devised, including polymer injection into the pancreatic duct, anastomosis of the duct to recipient bowel or anastomosis of the donor duodenum encompassing the pancreatic duct to recipient urinary bladder. The worldwide experience shows little difference in graft survival rates between these three techniques, while certain centers have yielded excellent results (74% 22-month graft survival) with the urinary drainage technique. This technique has been adopted in most centers in the country today.

Although the technical aspects of pancreas transplantation are difficult, the greatest obstacle to a successful outcome remains immunologic. Registry analysis accompanying various immunosuppressive therapy protocols shows that graft survival rates are highest (62% at one year for technically successful grafts) with the triple-therapy regimen (low-dose cyclosporine, azathioprine and prednisone). In addition, certain centers are using antilymphocytic globulin prophylactically to decrease the incidence of rejection.

A reliable indicator for the early diagnosis of pancreas graft rejection remains elusive. In patients who have had a simultaneous kidney and pancreas transplant, an elevated serum creatinine level precedes the development of hyperglycemia during a rejection episode of both organs. A distinct advantage of the urinary drainage technique is the ability to follow urinary amylase concentration as a monitor of pancreas graft function. A decrease in urinary amylase often precedes hyperglycemia as an indicator of rejection, and early treatment is initiated on this basis.

PATRICK SOON-SHIONG, MD
GEOFFREY WHITE, MD
*Los Angeles*

### REFERENCES

Gray DWR, McShane P, Morris PJ: A method for isolation of islets of Langerhans from the human pancreas. Diabetes 1984 Nov; 33:1055-1061

Sollinger HW, Belzer FO, Kalayoglu M: Urinary drainage in pancreas transplantation. Transplant Immunol Lett 1986 May; 3:1

Soon-Shiong P, Swafford G, Levin S: Successful long-term exocrine and endocrine function in the autotransplanted pancreas in man. Pancreas, in press

Sutherland DER, Kendell D, Goetz FC, et al: Pancreas transplantation. Surg Clin North Am 1986 Jun; 66:557-582

Valente U, Arcuri V, Barocci S, et al: Islet and segmental pancreatic autotransplantation after pancreatectomy: Follow-up of 25 patients for up to five years. Transplant Proc 1985 Feb; 17:363-365

## Alternatives to Total Mastectomy for Carcinoma of the Breast

MORE THAN 90 YEARS AGO Halsted introduced the radical mastectomy as the first rational approach to the surgical management of breast cancer. This procedure remained the most common operation for carcinoma of the breast until it was replaced by the modified radical mastectomy in which the

pectoralis major muscle is not removed, lessening the postoperative deformity. Because survival is not diminished by preserving muscle, the role of even less deforming techniques has been examined in light of our better understanding of the biology of breast cancer.

Removing the entire breast is based on the multifocality of breast cancer and the potential for involvement of the major lactiferous ducts near the nipple. Radiotherapists have long advocated treatment of the whole breast and nipple with external beam radiotherapy or implants, rather than by total breast removal. Early studies showed a high local recurrence rate with irradiation alone. Combining surgical therapy with irradiation, however, appeared as effective as radical mastectomy.

The medical community had been reluctant to accept these observations for a number of reasons, primarily because these trials were not prospective or randomized and they often relied only on clinical staging of the axilla. The highly variable nature of breast cancer and the number of prognostic factors involved made such studies difficult to evaluate. Recent prospective randomized trials have led to a wider acceptance of less-than-total mastectomy.

Veronesi and co-workers reported the first major prospective randomized trial comparing standard surgical treatment with a combination of a surgical procedure and modern radiotherapy. In this trial, patients were randomly selected for a Halsted radical mastectomy or quadrantectomy with axillary lymph node dissection and postoperative radiation therapy. Quadrantectomy removes the entire breast quadrant containing the tumor, including overlying skin and surrounding normal tissue. All entered into this trial had tumors less than 2 cm, not centrally located and no clinical evidence of axillary lymph node disease—the American Joint Committee on Cancer's tumor-node-metastasis stage $T_1N_0M_0$. All patients had accurate axillary staging by examination of the resected lymph nodes. There is no statistically significant difference in local control with either treatment and no difference in overall survival or disease-free survival in this trial comparing radical mastectomy with a far-less-deforming operation and radiotherapy.

The National Surgical Adjuvant Breast Project (NSABP) reported the findings of a trial that extend the observations of Veronesi and associates. In this trial, eligible patients could have a primary tumor as large as 4 cm with or without palpable axillary lymph nodes ($T_{1-2}N_{0-1}M_0$). Patients were randomly assigned to one of three different treatment modalities: the modified radical mastectomy; segmental mastectomy and axillary lymph node dissection, or segmental mastectomy, and axillary node dissection and postoperative irradiation. Unlike the quadrantectomy, the segmental mastectomy removes only the tumor and a small rim of surrounding normal tissue and is even less deforming. Among the 1,843 women randomly selected in this study, few local recurrences were actually seen in the mean follow-up period of 39 months. The lowest local failure rate is among patients treated with segmental mastectomy and radiation therapy. The actuarial predicted five-year local recurrence rate for segmental mastectomy plus irradiation is 7.7%. Segmental mastectomy without irradiation, however, has a predicted five-year local recurrence of 27.9%. No significant difference in overall survival or disease-free survival is seen among the three different forms of treatment. A longer follow-up will be necessary to answer the questions related to salvage mastectomy for local recurrences and the late effects of treatment.

These trials clearly show that treatment involving less than mastectomy combined with radiation therapy is effective in patients with $T_1$ and $T_2$ carcinoma of the breast. Treatment comprising less than total mastectomy without irradiation has a much higher local recurrence rate but may be acceptable for some patients, particularly the elderly, in whom radiation therapy is not desirable. The cosmetic results are far superior to those from mastectomy, and overall survival appears the same. It must be remembered that in both trials, all patients had infiltrating breast cancer, tumor-free margins at operation, tumors not centrally located and had an axillary dissection. Physicians must select their patients with caution, for there are certain groups who should not be considered for a breast-conserving operation. Patients with clinical multifocality, large tumors, centrally located tumors, involvement of the skin, nipple or areolar complex and inflammatory breast cancer or unusual histologies generally should not be treated in this manner.

ARMANDO GIULIANO, MD
*Los Angeles*

**REFERENCES**

Fisher B: The revolution in breast cancer surgery: Science or anecdotalism? World J Surg 1985; 9:655-666

Fisher B, Bauer M, Margolese R, et al: Five-year results of a randomized clinical trial comparing total mastectomy and segmental mastectomy with or without radiation in the treatment of cancer. N Engl J Med 1985 Mar 14; 312:665-673

Veronesi U, Zucali R, Luini A: Local control and survival in early breast cancer: The Milan trial. Int J Radiat Oncol Biol Phys 1986 Apr; 12:717-720

## Treatment of Renovascular Hypertension

GOLDBLATT 50 years ago produced systemic hypertension in dogs by constricting the renal artery. His published report in 1935 was the first to document a causal relationship between renovascular disease and hypertension. This landmark observation is the basis of our modern understanding of renovascular hypertension. It is now well recognized that significant renal artery stenosis may lead to hypoperfusion of renal parenchyma inducing inappropriate overproduction of renin. By means of the renin angiotensin axis, hypertension is produced.

Because renovascular hypertension is relatively uncommon, it is important to appreciate the clinical features that distinguish it from other forms of hypertension. These include severe diastolic hypertension (greater than 115 mm of mercury), an onset of severe hypertension abruptly and at the extremes of life, evidence of systemic atherosclerosis and the presence of an abdominal bruit. Additionally, this disorder appears to have a racial predilection, being more common in whites. Although these features are typical of patients with renovascular hypertension, the absence of one or more features does not exclude the diagnosis. In our experience, the most reliable clinical predictor of the disorder has been severe diastolic hypertension.

Anatomic and functional studies are required to establish the diagnosis. Arteriography is the primary diagnostic modality because less-invasive tests, such as rapid sequence intravenous pyelography and isotopic renography, are imprecise and nondiagnostic in approximately 50% of patients with this disorder. The functional significance of arteriographically shown renal artery stenoses is confirmed by selective renal vein renin assays, split renal function studies or both. These studies are essential, for only 50% of such lesions are functionally significant and the cause of a patient's hypertension.

We consider vascular reconstruction of the renal artery the preferred method of treatment for patients with renovascular hypertension. Recent studies report a mortality rate of 0.5% to 2% and a technically successful operative result in more than 95% of cases following revascularization. Cure of hypertension occurs in 40% and significant improvement in 51%. Also, revascularization preserves and in selected circumstances improves overall renal function. These salutary effects are long lasting, for a recent report with a 15-year follow-up documented excellent blood pressure control and a reduction in morbid events and death from cardiovascular causes following renal revascularization.

Medical management of the disorder has been aided by the recent development of specific angiotensin-converting enzyme inhibitors. Whether medical therapy using these inhibitors and the potent arsenal of other antihypertensive medications is comparable with surgical treatment is not known. Our preference for operative management is based on two reports prospectively contrasting surgical and medical treatment that have shown significant preservation of renal function, better control of hypertension and improved survival with surgical treatment.

Percutaneous transluminal angioplasty (PTA) of the renal arteries is a relatively new approach to treating renovascular hypertension. National experience and follow-up are limited, but short-term results approaching those of surgical treatment have been published for specific lesions. In particular, fibrodysplastic and segmental atherosclerotic stenoses appear to respond well to PTA. Conversely, atherosclerotic lesions affecting the ostia of the renal artery and diffuse atherosclerotic involvement of the renal artery respond poorly. The long-term outcome of such dilatations is unknown and awaits further study. At present, the exact role PTA will ultimately play in treating this disorder remains to be determined.

To distinguish patients with renovascular hypertension from the hypertensive population requires knowledge of the disorder's characteristic clinical presentation, a high index of suspicion and the use of anatomic and functional data. The ability of present treatment options to cure or significantly improve this particular form of hypertension with a subsequent reduction in morbid events makes it imperative for practicing physicians to do so.

FRED A WEAVER, MD
*Los Angeles*

#### REFERENCES

Dean RH: Renovascular hypertension. Curr Probl Surg 1985 Feb; 22:3-67

Dean RH, Englund R, Dupont WD, et al: Retrieval of renal function by revascularization: Study of preoperative outcome predictors. Ann Surg 1985 Sep; 202:367-375

Dean RH, Krueger TC, Whiteneck JM, et al: Operative management of renovascular hypertension. J Vasc Surg 1984 Jan; 1:234-242

Martin LG, Price RB, Casarella WJ, et al: Percutaneous angioplasty in clinical management of renovascular hypertension: Initial and long-term results. Radiology 1985 Jun; 155:629-633

Stanley JC, Ernst CB, Fry WJ (Eds): Renovascular Hypertension. Philadelphia, WB Saunders, 1984

## Anal-Sphincter Saving Operations

PRESERVATION of the anorectal sphincter mechanism and the lower segment of the rectal muscle after colectomy and removal of the rectal mucosa for certain benign disorders was described several decades ago and was applied to patients with ulcerative colitis in 1947. The endorectal pull-through procedure did not gain extensive clinical application until 1964, when it was used in conjunction with a colonic pull-through for Hirschsprung's disease. A resurgence of interest in the endorectal ileal pull-through procedure for ulcerative colitis and colonic polyposis has occurred during the past decade as a result of better clinical results after using more precise operative techniques. During the past ten years about 1,400 such operations have been carried out by surgeons at certain large medical centers in the United States and Europe.

The endorectal ileal pull-through was initially constructed without a reservoir. During the past ten years, however, because of stool frequency and urgency, a reservoir was incorporated in the lower end of the pull-through segment to serve as a storage area. A protective ileostomy for two to four months has been found essential to minimize the risk of postoperative pelvic infection. Three basic reservoirs have been used: the S-shaped, the J-shaped and the lateral isoperistaltic ileal reservoir. Although each of the various reservoirs has provided satisfactory functional results for most patients undergoing the operation, about 20% to 30% of patients have needed a repeat operation or have had less-than-optimal function after the operation. The lateral reservoir may be revised most easily.

The neurogenic sensory and discriminatory mechanisms remain largely intact, and good continence can be achieved if the rectal mucosa is removed down to the dentate line, providing the anorectal sphincter muscle is not disturbed. The length of the rectal muscle retained above the ileoanal anastomosis need not be longer than 4 to 5 cm. Long rectal muscle segments have caused compression of the ileal reservoir and in some cases produced acute angulation of the ileum or reservoir, contributing to the development of partial outlet obstruction with stasis and reservoir inflammation.

Certain patients with obesity, with tight anal sphincter spasm and those with severe rectal mucosal disease may do better postoperatively if the pull-through operation is constructed without a reservoir. If a reservoir is used, the configuration appears to be less important than the assurance that the reservoir is short enough to avoid stasis and that the spout extending to the ileoanal anastomosis is short. Although patients generally will have less fecal urgency, frequency and nocturnal soiling with a reservoir (mean, 6.5 movements per 24 hours in three months) than without a reservoir (mean, 9.8 movements per 24 hours in three months), by six months the

patients without a reservoir will have a similar number of movements as those with a reservoir (5 to 7 per 24 hours).

Long-term follow-up with close attention to a patient's bowel pattern will lead to early detection of reservoir enlargement, outlet obstruction, ileoanal anastomotic stenosis, peri-pull-through sinuses and other complications. Almost all of these problems are surgically correctable if treated early. Most medications can be discontinued within six months in patients who do not have complications. Patients may return to full physical activities including competitive sports within three to four months. Of 150 patients with the pull-through operation done in our hospital, 136 are currently functioning well; review of the last 100 consecutive patients shows that all but 2 are currently progressing well (98%), indicating the decreased number of complications as our clinical experience has increased. The endorectal ileal pull-through operation is technically difficult, but close attention to the many details of operative and postoperative care is likely to provide gratifying long-term results and a very satisfactory alternative to a permanent ileostomy or Kocks's pouch.

ERIC W. FONKALSRUD, MD
*Los Angeles*

REFERENCES

Fonkalsrud EW: Endorectal ileal pullthrough with isoperistaltic ileal reservoir for colitis and polyposis. Ann Surg 1985 Aug; 202:145-152

Martin LW, Fischer JE: Preservation of anorectal continence following total colectomy. Ann Surg 1982 Dec; 196:700-704

Metcalf AM, Dozois RR, Kelley KA, et al: Ileal 'J' pouch-anal anastomosis: Clinical outcome. Ann Surg 1985; 202:735-739

## Treatment of Asymptomatic Gallstones

THERE ARE THREE major issues in the treatment of asymptomatic gallstones. Should prophylactic cholecystectomy be done for asymptomatic gallstones? Are there any special factors that justify prophylactic cholecystectomy? Is incidental cholecystectomy indicated at laparotomy for another condition? Unfortunately, prospective and randomized trials to answer these questions have not been done.

Arguments used to justify prophylactic cholecystectomy include the "high" incidence of the likely development of symptoms or complications and the "small" risk of carcinoma of the gallbladder developing. The risk of carcinoma is so small that it is not an issue. In a study by Gracie and Ransohoff, the likelihood of symptoms developing in patients found to have asymptomatic gallstones was apparently 2% per year; this figure plateaued off so that at 15 years only 18% of patients became symptomatic. In those persons who become symptomatic, generally biliary colic occurs rather than a complication so that there does not appear to be increased morbidity or mortality in delaying cholecystectomy until symptoms appear. Therefore, it is difficult to justify prophylactic cholecystectomy for the average patient with asymptomatic gallstones.

Special factors reportedly increase the risk of complications of gallstones, thereby justifying prophylactic cholecystectomy. These include diabetes mellitus, nonvisualization of the gallbladder on oral cholecystography, stones larger than 2 cm, a calcified gallbladder, young age, patients requiring immunosuppression and pigmented stones associated with hemolytic anemias. Although reasonable arguments can be made for prophylactic cholecystectomy under these conditions, firm data are lacking. Diabetes, which according to surgical dogma is a risk factor for an adverse outcome in gallbladder disease, has recently been questioned as being an independent risk factor. Although most likely some risk factors justify prophylactic cholecystectomy, one has to fall back on clinical judgment rather than firm data in making a decision. It would generally be prudent to recommend prophylactic cholecystectomy in a relatively young patient with another of the aforementioned risk factors.

Finally, despite my personal aversion to incidental procedures during laparotomy for another reason, incidental cholecystectomy does seem to be reasonable as long as great care is taken against contamination.

RICHARD A. CRASS, MD
*Portland, Oregon*

REFERENCES

Gracie WA, Ransohoff DF: The natural history of silent gallstones—The innocent gallstone is not a myth. N Engl J Med 1982; 307:798-800

Sandler RS, Maule WF, Baltus ME: Factors associated with postoperative complications in diabetics after biliary tract surgery. Gastroenterology 1986; 91:157-162

Schubert TT: Hepatobiliary system in sickle cell disease. Gastroenterology 1986; 90:2013-2021

## Fine-Needle Aspiration of Thyroid Nodules

FINE-NEEDLE ASPIRATION of thyroid tumors is an increasingly popular method of obtaining a preoperative cytologic diagnosis and determining the malignant potential of a thyroid mass. In addition, other thyroid abnormalities such as chronic lymphocytic thyroiditis can be cytologically confirmed. Many large series have shown that fine-needle aspiration of the thyroid can be done with a high degree of safety and clinical specificity. These series show that cytologically unsatisfactory specimens occur in about 15% to 20% of aspirates. With proper physician training and experienced cytologists, false-negative rates of 2% and false-positive rates of about 20% can be achieved.

Comparative studies of fine-needle aspiration with large-needle (TruCut) or drill-needle biopsies have shown that fine-needle aspiration may have a higher diagnostic yield than the other large-needle techniques. The overall accuracy of fine-needle aspiration of the thyroid gland depends on the ability of the physician doing the aspiration, the adequacy of specimen preparation and the experience of the cytologist.

The role of fine-needle aspiration biopsy does not need to be limited to specialized referral centers, but does require that the cytologist and the physicians doing the procedures become proficient with this technique. Complications have been reported in most series, but these have been relatively benign. In addition to the diagnosis of primary thyroid neoplasms, fine-needle aspiration may also show the presence of lymphoma or metastatic carcinoma. Adding monoclonal antibody examination to the routine cytologic preparations may improve the overall accuracy and expand the indications for the fine-needle technique.

Currently, fine-needle aspiration biopsy of the thyroid should be considered a valuable diagnostic tool in the preoperative evaluation of a thyroid nodule. When the physician

and the interpreting pathologist are well trained and comfortable with this technique, a high degree of accuracy should be obtained. We recommend fine-needle aspiration of thyroid nodules as the initial diagnostic test in evaluating thyroid tumors. All suspicious lesions should be surgically excised, and the failure to obtain adequate diagnostic material on needle biopsy or the failure of a "cold" nodule to respond to suppressive therapy mandates surgical excision.

EUGENE A. WOLTERING, MD
*Portland, Oregon*

#### REFERENCES

Boey J, Hsu C, Wong J, et al: Fine-needle aspiration versus drill-needle biopsy of thyroid nodules: A controlled clinical trial. Surgery 1982 Jun; 91:611-615

Schmid KW, Hofstadter F, Propst A Jr, et al: A fourteen year practice with the fine needle aspiration biopsy of the thyroid in an endemic area. Pathol Res Pract 1986 Jun; 181:308-310

Silverman JF, West RL, Larkin EW, et al: The role of fine-needle aspiration biopsy in the rapid diagnosis and management of thyroid neoplasm. Cancer 1986 Mar 15; 57:1164-1170

## Heart and Heart-Lung Transplantation

HEART TRANSPLANTATION has evolved from a clinical trial in 1968 to a therapeutic option in 1987 for patients with end-stage heart disease. To place the acceptance of heart transplantation in perspective, 62 heart transplants were done in 1981 as compared with 719 in 1985. The success of heart transplantation has been greatly improved with advances in immunosuppression. Before the use of cyclosporine, the one-year survival in 1980 was 63%. In 1987, one-year survival has increased to 82%.

With improved survival, age criteria for transplantation have been modified. Before 1980, patients older than 50 years were not considered. Currently patients to the age of 60 are thought to be reasonable candidates depending on their "physiologic" age. Infants and children are now being transplanted with the same expected survival rate as adults. Patients in cardiogenic shock are being maintained with the left ventricular assist device or the total artificial heart; 30% to 50% of them go on to successful cardiac transplantation.

In 1981 heart-lung transplantation was introduced as a therapeutic possibility for patients with irreversible pulmonary hypertension. The program at Stanford continues to evolve. So far, 41 heart-lung transplants have been done, 19 for primary pulmonary hypertension, 21 for Eisenmenger's complex and retransplantation in 1 patient with graft failure. Survival continues to improve with an actuarial survival rate of 65% and 54% at one and three years, respectively. Improved survival has come with better graft protection during organ recovery and a lower perioperative mortality from 28% in 1984 to 12% currently.

Potential heart-lung recipients are patients with primary pulmonary hypertension, congenital heart disease with Eisenmenger's physiology, fibrosing alveolitis and pulmonary fibrosis. Our criteria have recently expanded to include patients with cystic fibrosis.

At present, clinical heart-lung transplantation is limited by donor availability. Only 10% to 15% of the patients evaluated for organ recovery will be suitable for heart-lung donation. Aspiration or neurogenic pulmonary edema are ordinarily responsible for this low yield.

The future of heart and heart-lung transplantation will be influenced by improved immunosuppressive therapy, the use of mechanical devices as a bridge to transplant and, more importantly, by an increased number of available donor organs. As the public and the medical profession become more aware of the efficacy of transplantation, a stronger commitment to organ donation may be expected to provide an increasing number of patients with end-stage organ failure hope for survival through transplantation.

VAUGHN A. STARNES, MD
NORMAN E. SHUMWAY, MD
*Stanford, California*

#### REFERENCES

Borel JF, Feurer C, Gubler HU, et al: Biological effects of cyclosporin A: A new antilymphocytic agent. Agents Actions 1976; 6:468-475

Over PE, Stinson EB, Jamieson SE, et al: Cyclosporin-A in cardiac allografting: A preliminary experience. Transplant Proc 1983; 15:1247-1252

Starnes VA, Jamieson SW: Current status of heart and lung transplantation. World J Surg 1986; 10:442-449

## Brain Death

VICTIMS of profound and irreversible brain damage now survive longer because of improved critical care. In 1968 the ad hoc committee of Harvard Medical School published its definition of irreversible coma, which clinically defined brain death. In recent years, it has become apparent that this definition, which requires that the entire central nervous system (CNS) is functionless, is not always helpful clinically. The critical determination is not whether CNS demise has already occurred, but the establishment that this demise is inevitable. Brain death inevitably follows brain-stem death, and this death is a process, not an event. It has now become clear that spinal reflexes, auditory evoked brain-stem potentials and electroencephalographic activity can persist after CNS death. The persistence of these neurologic functions does not alter the inevitability of death, but it often complicates the decision to terminate support.

The prompt and accurate diagnosis of brain death is extremely important. To continue artificial support following brain death deprives a patient of a dignified death and needlessly prolongs the anguish of relatives. Continued support exhausts precious health care resources that could be used to care for patients with a possibility of recovery. For successful transplantation, brain death must be established before organ deterioration precludes harvesting, but physicians involved in the transplant procedure cannot certify brain death. Last, a clear definition of brain death is important for legal reasons.

The criteria for brain death rest on four important principles: (1) irreversible structural damage to the CNS shown by computed tomographic scanning or magnetic resonance imaging; (2) factors that depress the brain stem must be excluded—alcohol and barbiturates, muscle relaxants, hypothermia and gross metabolic imbalance; (3) the absence of brain-stem reflexes—corneal, pupillary, gag and oculovestibular, and (4) the absence of respiratory effort during a satisfactory apnea trial. If any of these criteria cannot be fulfilled, a confirmatory test to show the absence of cerebral blood flow is mandatory. These include radionuclide flow studies, digital intravenous arteriography and standard four-vessel cerebral angiography. The choice of which test to use is largely based

on individual physician preference and institutional support. A portable bedside flow scan is fast and convenient, but the other tests are acceptable substitutes.

Scrupulously adhering to these principles and criteria allow physicians to provide compassionate care to both patient and family while maximizing the use of hospital resources and availability of organs for transplantation and minimizing medicolegal risk.

A. CRAIG EDDY, MD
CHARLES L. RICE, MD
*Seattle*

**REFERENCES**

Ad Hoc Committee of the Harvard Medical School to Examine the Definition of Brain Death: A definition of irreversible coma. JAMA 1968; 205:337-340

Goodman JM, Heck LL, Moore BD: Confirmation of brain death with portable isotope angiography: A review of 204 consecutive cases. Neurosurgery 1985 Apr; 16:492-497

Outwater KM, Rockoff MA: Apnea testing to confirm brain death in children. Crit Care Med 1984 Apr; 12:357-358

Ropper AH, Kennedy SK, Russell L: Apnea testing in the diagnosis of brain death. J Neurosurg 1981; 55:942-946

Vatne K, Nakstad P, Lundar T: Digital subtraction angiography (DSA) in the evaluation of brain death: A comparison of conventional cerebral angiography with intravenous and intraarterial DSA. Neuroradiology 1985; 27:155-157

## ADVISORY PANEL TO THE SECTION ON GENERAL SURGERY

NORMAN CHRISTENSEN, MD
*Advisory Panel Chair*
*CMA Scientific Board Representative*
*Eureka*

WILLIAM E. TRUMBULL, MD
*CMA Section Chair*
*Section Editor*
*Santa Monica*

A. R. MOOSSA, MD
*CMA Section Secretary*
*University of California, San Diego*

ALLEN H. JOHNSON, MD
*CMA Section Assistant Secretary*
*San Jose*

BRUCE W. BRANSON, MD
*Loma Linda University*

JOHN A. COLLINS, MD
*Stanford University*

F. WILLIAM BLAISDELL, MD
*University of California, Davis*

G. ROBERT MASON, MD
*University of California, Irvine*

HERBERT I. MACHLEDER, MD
*University of California, Los Angeles*

HAILE DEBAS, MD
*University of California, San Francisco*

ARTHUR J. DONOVAN, MD
*University of Southern California*

EARL F. WOLFMAN, MD
*Sacramento*

RONALD TOMPKINS, MD
*Los Angeles*

ROBERT BARONE, MD
*San Diego*

# Editorials

## Contemporary Aims for American Medicine

ELSEWHERE in this issue is the editor's report on the recent WJM forum on "The Aim of American Medicine Within the Constraints of Today's Society." As the report indicates, three aims rather than one seemed to emerge. The first, caring for patients, was a reaffirmation of what has been the raison d'être of physicians throughout history. The second, seeking good health for all, seems a more modern goal. And the third, perhaps a more avant garde idea, is that physicians can begin to use their special professional knowledge and intimate human experience to help others to find an appropriate balance when there are conflicting indications or purposes, in whatever arena, that relate somehow to health or health care. This latter aim, while perhaps new, can also be viewed as just another dimension of patient care. In fact the process to be used is quite similar to what physicians are trained to do, and do all the time when they have to balance all the conflicting factors in the technologic and human equation with a sick, injured or emotionally disturbed patient.

Or, if one preferred to consider only one aim, the forum results could be interpreted in another way. The basic aim of physicians, and therefore of the medical profession, would, in this interpretation, be to use their professional knowledge and practical experience with the human condition to achieve three purposes: (1) to provide caring and curing for the sick, (2) to seek better health for all and (3) to assist patients and society as a whole to balance conflicting needs and purposes as these pertain to health. In this interpretation, doctors should not only function as physicians to patients, but individually and collectively they should act as physician to society whether in the community, state or nation, or in the case of the nuclear threat, the world. They would also offer their expertise to help find a reasonable balance when conflicts between these two goals occur.

What seems to be needed now is a resounding reaffirmation of what medicine is all about, an even more resounding rejection of the devilish idea that dollars (the bottom line) should come first with caring in second place or even last, and then, beyond this, a conscious determination is needed to adapt the professional skills of physicians and the medical profession so as to help promote better health for all, and for the profession as a whole to develop and play a larger, and perhaps in some ways a newly defined, role as physician to society.

MSMW

## Differentiating Treatable Causes of Dementia

THE SUBJECT of treatable dementia is most timely in an era of the vastly increasing segment of the aged in California and the nation. Mahler, Cummings and Benson have provided us in this issue with an excellent and comprehensive review that includes guidelines both for the recognition of reversible dementias and approaches to their treatment. Their report of treatable dementia is consistent with findings in the Alzheimer Center at the University of California, San Francisco, a tertiary clinical setting for diagnostic consultation and continuing assistance for patients with Alzheimer's disease and their families. With a few exceptions, the diagnosis of Alzheimer's disease had previously been made for the patients at this setting. A recent unpublished review of 68 consecutive patients examined there revealed that 25% of them did not have any dementing illness and were suffering in large part from affective disturbances. Very similar findings have been reported by Steel and Feldman[1] at Queens Square Hospital in London where 20% to 25% of their sample had a probably treatable illness, the most common of which was depression.

The authors note that most of the diseases of the extrapyramidal system result in cognitive and emotional difficulties. There has also been some disagreement about the degree to which there are distinguishing features between dementia resulting from cortical or subcortical involvement. In a recent study, Huber and co-workers concluded that the subcortical diseases are associated with less severe decline of intellectual and memory features and tend to show less aphasia, apraxia and agnosia than are observed in Alzheimer patients.[2] It was concluded that the subcortical illnesses were quantitatively and qualitatively different from cortical dementias and that clinical manifestations provide diagnostic and potential treatment leads.

Reisberg has suggested a systematic approach to identifying reversible causes of dementia using the approach of functional assessment staging.[3] Although he notes that more longitudinal studies of Alzheimer's are needed to better clarify the clinical progression of Alzheimer's disease, he believes that most Alzheimer patients have a characteristic progression of impairment. He has attempted to outline the characteristics of this gradual progression and postulates that if a symptom appears out of sequence, it may suggest the presence of a treatable complication of Alzheimer's disease or even a different diagnosis. It is his assumption that the course of Alzheimer's disease is predictable and that complications of other illnesses that may be reversible can be differentiated from the usual and normal progression of Alzheimer's disease.

Several approaches to differentiating reversible dementias have been studied and have not proved sufficiently promising. Dexamethasone suppression, for example, was found in 38% of a depressed group of elderly persons without evidence of dementia, but was also found in 17% of a sample of demented patients who were not depressed.[4] Similarly disappointing have been attempts to associate P3 latency in event-related potentials.[5] The importance of perfusion imaging for assessment and differential diagnosis of Alzheimer's disease is still in an early stage of development and merits further study.

The tables in the article by Mahler and coauthors are especially complete and merit continuing review in the differential diagnosis of cognitive disturbance in the elderly. It is probable that in the interest of completeness within the limits of brevity, depression, the most treatable entity which tends to be confused with dementia, receives relatively little more emphasis than other, rather rare, treatable dementias.

Roth recently cited depression as the most common single cause of complaints of impaired memory in later life.[6] He further noted that it is regularly accompanied by mild cognitive dysfunction and difficulty in concentration. He cited the

following characteristics of depression that showed dementia in addition to those noted by Mahler and co-workers:

- Onset more clearly identifiable in time
- Brief duration, usually 6 to 12 months
- Personal and family histories of depressive illness
- The use of a range of complex skills in everyday tasks
- Circumscribed and inconsistent memory impairment
- Information often assimilated and used efficiently
- Usually detailed complaints of cognitive dysfunction
- Emphasis of disability
- Little effort made to do even simple tasks
- No effort to keep up by means of notes and calendars
- Pervasive affective change; depressive response to minor or major adversity
- Complaints may be inconsistent with observed behavior
- Intermittently or consistently good rapport in clinical examination
- Distress in response to failure in performance
- Pronounced fluctuations between normality and impairment
- Nocturnal accentuation uncommon.

Mahler and colleagues emphasize the need for the detection and amelioration of treatable causes of dementia to avoid further deterioration and, where the disease is irreversible, to offer assistance with treatable complications and thereby increase comfort. This emphasis merits strong support in that once a diagnosis of Alzheimer's or other irreversible dementia is made, there tends to be a legacy of labeling with less zeal or motivation for further study, care or treatment. It is evident that a diagnosis of irreversible dementia should only be made with great care. The effects of such news on both patient and family are enormous.

There frequently tends to be an aura of therapeutic nihilism in the care and treatment of patients with irreversible progressive dementia. Mahler and co-workers very appropriately note that where treatment cannot reverse or halt the disease process, therapy may maximize remaining ability and prevent unnecessary complications. Probably the most common complaint of families of elderly patients with persistent intellectual impairment reflects their frustration because of the lack of direction or assistance from the medical community once the diagnosis has been established. There is respect for the interest and expertise in diagnostic formulation, but this may end at times in anger at what is perceived as inadequate subsequent attention and care.

There are, however, a number of avenues of assistance which may be offered. Individual and family counseling helps to provide assistance with planning and decision making. It is also often necessary to deal with emotional reactions of family members who live with a demented relative. In contrast with other psychotherapeutic or counseling situations, the emphasis is often on assisting the caregivers to understand why the patients behave as they do, and that the usual rules and guidance for behavior often do not apply to a demented person. Furthermore, adjustments are constantly necessary to deal with increasing incapacity and resultant behavior problems. Family counseling may also focus on the problems family members are experiencing in their interaction with a cognitively impaired relative and the evolution of coping strategies. In addition, the family may often need assistance to accept appropriate help, which is often available in the community, both for themselves and for the patient, and thus strengthen the support network. There is often conflict and dissension within a family with respect to issues of care and treatment, and a focus of counseling may be the resolution of such issues.

The physical setting plays an important role in either inhibiting or encouraging certain behaviors. Clinical nurse specialists who are trained in gerontology can make home visits to help adapt the home to the capacities of an impaired person and to suggest environmental changes. Prompt attention can also be paid to health care and medical problems. Self-help groups are playing an increasingly important role for elderly cognitively impaired persons, and families should be acquainted with them. Finally, assistance may be provided for the consideration of alternative settings when an impaired patient can no longer be cared for at home. There is also available a range of social services to these patients and their families, to acquaint them with appropriate social agencies and professionals which are often available in the community and which may be of inestimable help.

Families of an elderly cognitively impaired relative are tremendously grateful for such assistance in these areas, for which they very often have no information.

Roth has pointed out that one of the most important differences in psychiatric disturbance between the young and the elderly is the relative silence of these diseases in the elderly.[6] He notes that this is true of many other medical illnesses—such as a lower temperature of the constitutional disturbances—and might be anticipated in a subtler and more complex connection between physical illness and psychiatric disorder. This difference emphasizes the pitfalls in differential diagnosis and highlights the need for more careful evaluation of an elderly cognitively impaired patient, as well as greater awareness of pathways for cure and caring.

It has been said that "there is nothing more demoralising than the tired rattling of a demented brain. . . . Tiny ghettos of memory walled in with confabulations against the oppression of empty space."[7] Any efforts to assist in the treatment of reversible dementia or in alleviating the burdens of patients and their families who face this situation most certainly merit our earnest attention and involvement.

LEON J. EPSTEIN, MD, PhD
*Langley Porter Psychiatric Institute*
*University of California, San Francisco, School of Medicine*
*San Francisco*

#### REFERENCES

1. Steel K, Feldman RS: Diagnosing dementia and its treatable causes. Geriatrics 1978; 979:79-88

2. Huber SJ, Shuttleworth EC, Paulsen GW, et al: Cortical vs subcortical dementia: Neuropsychological differences. Arch Neurol 1986; 43:392-394

3. Reisberg G: Dementia: A systematic approach to identifying reversible causes. Geriatrics 1986; 41:30-46

4. Georgetas A: Dexamethasone suppression in dementias, depression, and normal aging. Am J Psychiatry 1986; 143:452-456

5. Kraivhin C, Gorden E, Meares R, et al: Psychometrics and event-related potentials in the diagnosis of dementia. J Gerontol 1986; 41:154-162

6. Roth M: Differential diagnoses of psychiatric disorders in old age. Hosp Pract 1986; 21:111-138

7. Cox IG: Treating diabetes and dementia. Br J Clin Res 1983; 287:131-132

# Case Reports

## Reversible Renal Resistance to Aldosterone Associated With Interstitial Nephritis

JOHN J. REGAN, Jr, MD
CHARLES S. GREENBERG, MD
ARSHAG D. MOORADIAN, MD
NANCY STALEY, MD
FRANK Q. NUTTALL, MD, PhD
*Minneapolis*

ASCENDING PARALYSIS of metabolic origin has been described in renal failure,[1] hyperkalemic paralysis,[2] during spironolactone therapy[3] and in Addison's disease.[4] Our patient presented with ascending flaccid quadriplegia and was found to have an acquired form of pseudohypoaldosteronism associated with interstitial nephritis. He was sequentially treated with cephalothin sodium and tobramycin sulfate therapy but suffered no other recognized renal insult. The abnormality resolved spontaneously over the course of six months.

### Report of a Case

A 50-year-old man was admitted to the Minneapolis Veterans Administration Medical Center (VAMC) for treatment of a pelvic fracture sustained in a motorcycle accident. His medical history included ischemic heart disease for which a triple-vessel coronary artery bypass had been done two years earlier. Renal function had been normal. There was no family history of kidney disease.

Before admission, his medications consisted of digoxin, 0.25 mg daily; isosorbide dinitrate, 20 mg four times a day; propranolol hydrochloride, 80 mg four times a day, and two Dyazide capsules (Smith Kline & French, Carolina, PR)* twice a day. The patient had been on a salt-restricted diet and used a salt substitute.

On the day of admission, the blood pressure was 78/64 mm of mercury, pulse rate was 106 beats per minute and respirations were 23 per minute. A roentgenogram of the pelvis showed a fracture of the left ilium extending through the acetabulum with separation of the symphysis pubis. An intravenous pyelogram showed normal renal architecture with elevation of the bladder by a pelvic hematoma. The urine was grossly bloody. Laboratory studies elicited the following values: hematocrit 31.4%, leukocyte count 10,000 per $\mu$l and prothrombin time 12.8 seconds. The serum sodium was 145, the potassium 3.9, the chloride 108 and the carbon dioxide content 22 mEq per liter. The blood urea nitrogen was 22 and the glucose 172 mg per dl. Abdominal paracentesis showed gross blood. The patient had an exploratory laparotomy under general anesthesia and 1,000 ml of bloody fluid was found in the abdominal cavity; a ruptured viscus, however, could not be identified. The patient received 17 units of blood. Postoperatively, congestive heart failure developed, which responded to a regimen of furosemide, digoxin and salt restriction.

The patient had received cephalothin, 1 gram intravenously, every six hours since admission. On the 11th hospital day he had an episode of sepsis. Urine and blood cultures showed *Proteus morganii* sensitive to tobramycin. He was treated with tobramycin, 80 mg given intravenously every eight hours for four days, followed by an additional six days of therapy at the same dosage schedule administered intramuscularly. During this interval, tobramycin blood concentrations were in the therapeutic range. A decline in the serum sodium concentration was retrospectively noted on the fifth day of tobramycin therapy. At the cessation of tobramycin therapy, the serum sodium level was 131 and the serum potassium 6.2 mEq per liter. During this interval he had been on a 2-gram sodium diet and his urine output was 2.0 to 2.4 liters per 24 hours.

On the morning of the 23rd hospital day, the patient awoke with perioral numbness and nausea. During the next 12 hours a progressive ascending paralysis developed. He appeared dehydrated with poor skin turgor. There were no spontaneous movements in his extremities and he felt short of breath. With the patient in the supine position, the blood pressure was 110/70 mm of mercury, the pulse rate was 98 beats per minute and the respirations were 20 per minute and shallow. The central venous pressure was 0 cm of water. On neurologic examination he had a flaccid quadriplegia, with preservation of sensory function except for diminished sensation to light touch. Cranial nerve function was intact. Deep tendon reflexes were absent. A myelogram was normal.

Laboratory values were as follows: serum sodium 99, potassium 8.3, chloride 75 and $CO_2$ content 17 mEq per liter; blood urea nitrogen 67, creatinine 1.7 and calcium 9.7 mg per dl. The arterial blood pH was 7.4, partial pressure of oxygen was 74 torr, partial pressure of $CO_2$ was 25 torr and bicarbonate was 16 mEq per liter. An electrocardiogram showed only nonspecific ST changes and no evidence of hyperkalemia. An analysis of urine revealed occasional leukocytes, 5 to 10 erythrocytes, no casts and mild proteinuria. The specific gravity was 1.020 and pH 5.0. The 24-hour creatinine clearance was 72 ml per minute. The protein content in a 24-hour urine collection was 2.5 grams. Bence Jones protein and light chains were not present. The urine sodium level was 40 mEq per liter, urine potassium 45 mEq per liter and urine osmolality 414 mosm per kg.

A presumptive diagnosis of adrenal insufficiency was made and the patient was treated with a saline infusion and intravenous administration of hydrocortisone. The paralysis cleared rapidly in a descending manner after two hours. After ten hours the serum sodium level had increased to 122 mEq

ABBREVIATIONS USED IN TEXT

ATPase = adenosine triphosphatase
Ig = immunoglobulin
VAMC = Veterans Administration Medical Center

*Each capsule contains triamterene, 50 mg, and hydrochlorothiazide, 25 mg.

(Regan JJ Jr, Greenberg CS, Mooradian AD, et al: Reversible renal resistance to aldosterone associated with interstitial nephritis. West J Med 1987 Jun; 146:742-745)

From the Section of Endocrinology, Veterans Administration Medical Center, and the Departments of Medicine and Pathology, University of Minnesota Medical School, Minneapolis.

Reprint requests to Arshag D. Mooradian, MD, VA Medical Center (11E), 16111 Plummer St, Sepulveda, CA 91343.

per liter and the serum potassium concentration had fallen to 5.3 mEq per liter. The central venous pressure was 4.0 cm of water. Subsequent testing of renal and adrenal function is described below.

## Methods

The renin-aldosterone system and renal salt handling were evaluated in the Special Diagnostic and Treatment Unit of the Minneapolis VAMC. Unless otherwise noted, diuretic therapy was withheld at least ten days before study. Serum cortisol was measured by a competitive protein-binding assay. Plasma renin activity was determined using a New England Nuclear angiotension I radioimmunoassay kit. Serum and urine aldosterone was measured by the Mayo Medical Laboratories.

Kidney tissue obtained by percutaneous needle biopsy was studied by light, electron and immunofluorescent microscopy. Tissue for light microscopy was fixed in 10% buffered formalin and 2-micron sections were stained with hematoxylin-eosin, Masson's trichrome, periodic acid-Schiff and Jones's silver stain. Tissue for electron microscopy was fixed with 3% glutaraldehyde in 0.1 mol per liter phosphate buffer, dehydrated in alcohol and embedded in Epon. These sections were stained with uranyl acetate and lead citrate and examined with an RCA EMU-4 electron microscope. Tissue for immunofluorescence was snap-frozen in isopentane precooled in liquid nitrogen. For direct immunofluorescent staining, 2-micron cryostat sections were fixed in acetone, washed in phosphate-buffered saline and incubated at 37°C for 30 minutes. The fluorescein-labeled antiserum used was specific for immunoglobulin (Ig) G, IgM, IgA, complement C3, fibrinogen and albumin (Hyland Laboratories, Costa Mesa, California). Sections were examined with a Zeiss Universal microscope equipped with a mercury-vapor light source and appropriate filters.

## Results

*Adrenal Cortical Function Testing*

On the 39th hospital day, while the patient was receiving intravenous saline and dexamethasone, a four-hour adrenocorticotropic hormone infusion (0.25 mg cosyntropin) test was done. Serum cortisol increased from 6.6 μg per dl to 30 μg per dl. The same study was repeated the following day and again was negative, the serum cortisol rising from 8.3 to 40 μg per dl. There was a simultaneous increase of the serum aldosterone from 17 ng per dl to 32 ng per dl.

*Renin-Aldosterone Sodium Excretion Studies*

After electrolyte and water deficiencies had been corrected, the patient began a diet providing 120 mEq sodium and 60 mEq potassium daily. While on this high sodium diet, his supine renin level was elevated at 54 ng per ml per hour, the serum aldosterone level was 113 ng per dl, the urine aldosterone excretion was 220 μg per 24 hours and the sodium excretion was 195 mEq per 24 hours (Table 1).

To stimulate the renin-aldosterone system, the diet was switched to 10 mEq sodium and 60 mEq potassium, and a 40-mg dose of furosemide was administered. On the third day of this diet, the supine renin activity was 259 ng per ml per hour, the serum aldosterone level was 195 ng per dl, the urine aldosterone excretion was 160 μg per 24 hours and the sodium excretion was 195 mEq per 24 hours despite the elevated

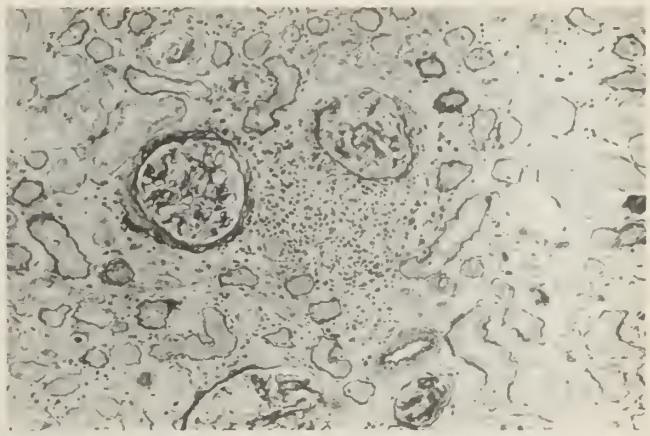


**Figure 1.**—Needle biopsy of kidney on low magnification shows focal interstitial lymphocytic infiltrates, diffuse mild interstitial fibrosis and periglomerular fibrosis (periodic acid-Schiff stain, reduced from a magnification × 300).

aldosterone levels. The study was terminated when the serum sodium level had decreased to 118 mEq per liter and the serum potassium had increased to 6.0 mEq per liter. The patient's condition precluded studies in an upright posture.

Two weeks later another study was undertaken to measure the effect of exogenous mineralocorticoid on sodium excretion while the patient was on a low sodium diet. At the beginning of this study, the serum electrolytes were normal. He was placed on a diet containing 10 mEq sodium and 60 mEq potassium. Similar elevations of plasma renin, serum aldosterone, urine aldosterone and urine sodium excretion were again noted. On the third day of this diet, he was started on a regimen of fludrocortisone acetate, 0.1 mg every six hours for two days; on the second day of fludrocortisone therapy the plasma renin activity was 101 ng per ml per hour, the serum aldosterone level was 153 ng per dl, the urine aldosterone excretion was 301 μg per 24 hours and the sodium excretion was 167 mEq per 24 hours. His weight had decreased by 1.5 kg, the serum sodium level had decreased to 126 mEq per liter and the serum potassium level had increased to 5.6 mEq per liter. These data show that although salt restriction was able maximally to increase the levels of plasma renin activity, serum aldosterone concentration and the aldosterone excretion rate, his kidneys were unable to respond by conserving sodium. Similarly, exogenous mineralocorticoid was unable to cause a reduction in the renal salt wasting. While on a high salt intake, however, the patient felt entirely well and his serum electrolyte levels returned to normal.

He was again studied 122 days after the initial admission. On the third day of a diet supplying 120 mEq of sodium and 60 mEq of potassium, his supine renin activity was 0.6 ng per ml per hour, increasing to 1.0 ng per ml per hour after four hours in the upright posture; the urine aldosterone excretion was 1 μg per 24 hours and the sodium excretion was 148 mEq per day. These responses were considered to be physiologic. A 40-mg dose of furosemide was given and the daily dietary sodium was restricted to 10 mEq. On the third day of this diet, the supine renin was 2.8 ng per ml per hour and increased to 11.0 ng per ml per hour after four hours in the upright posture. The urine aldosterone excretion increased to 25 μg per 24 hours and the sodium excretion decreased to 27 mEq per day. These results show a return to normal of the plasma renin activity and aldosterone excretion rate. When challenged by salt restriction, the hormones increased to appropriate levels

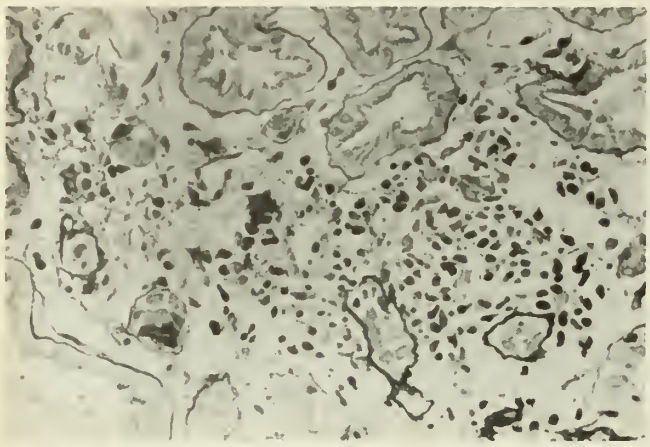


**Figure 2.**—Higher magnification of the kidney biopsy shows focal destruction of tubules associated with interstitial lymphocytic infiltrates (periodic acid-Schiff stain, reduced from a magnification × 410).

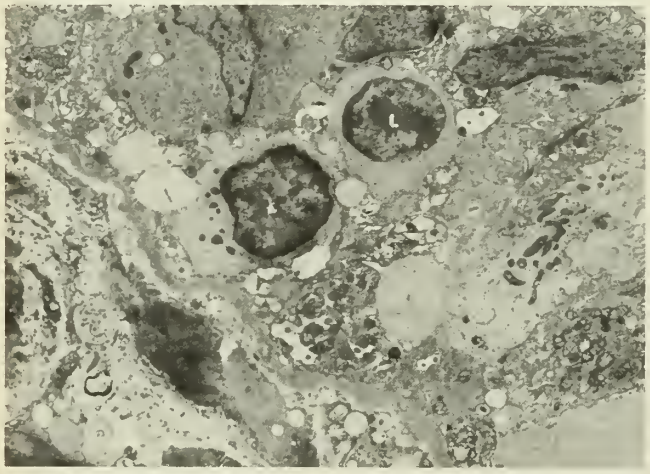



**Figure 3.**—Electron microscopy shows dense interstitial collagen and lymphocytes **(L)** infiltrating tubular epithelium (uranyl acetate and lead citrate, reduced from a magnification × 6,750).

and effected conservation of urinary sodium, indicating healing of the functional renal lesion.

*Pathology*

The needle biopsy specimen of the kidney taken 130 days after his initial hospital admission showed an interstitial nephritis characterized by focal interstitial mononuclear cell infiltrates, interstitial fibrosis, tubular atrophy and periglomerular fibrosis (Figure 1). The cellular infiltrate consisted primarily of lymphocytes, with scattered plasma cells. There were several areas of focal necrosis of tubular epithelium (Figure 2). Collections of sloughed epithelium were present in the lumens of a few tubules. Glomeruli were unremarkable. Direct immunofluorescent staining for immunoglobulins and C3 in glomeruli or tubules was negative. Electron microscopy confirmed the presence of dense interstitial fibrosis and interstitial lymphocytic infiltrate. Tubules showing lymphocytes infiltrating tubular epithelium were rare (Figure 3).

## Discussion

Pseudohypoaldosteronism has been described as a syndrome of salt wastage, primarily occurring in children and characterized by very high aldosterone excretion rates and high plasma renin activity. In the classic form, patients do not respond to exogenous salt-retaining drugs[5]; however, a group of children has been described that did respond to salt-retaining steroids.[6] There also is a report of a congenital proximal and distal tubular sodium-potassium adenosine triphosphatase (ATPase) deficiency.[7] Severe salt wasting in adults has been attributed to a decreased number of tubules that are unresponsive to elevated aldosterone levels. Renal tubular resistance to aldosterone has been recognized in patients with systemic lupus erythematosus with normal plasma renin activity.[8,9] Rado and co-workers described the case of a patient with chronic interstitial nephritis of unknown cause with renal tubular acidosis and hyperkalemia unresponsive to massive doses of aldosterone.[10] Cogan and Arieff described a patient in whom renal resistance to aldosterone developed as a

TABLE 1.—*Renin-Aldosterone Sodium Excretion Studies*

| Days Elapsed From Initial Hospital Admission | Dietary Sodium Content, mEq/24 h | Serum Creatinine, mg/dl | Serum $CO_2$ Content, mEq/liter | Serum Potassium, mEq/liter | Urinary Sodium Excretion, mEq/24 h | Urinary Potassium Excretion, mEq/24 h | Plasma Renin Activity, ng/ml/h | | Serum Aldosterone, ng/dl | Urinary Aldosterone, µg/24 h |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | Supine | Erect | | |
| | | | | | | | Normal <3.0 on High $Na^+$ Diet | Normal >1.3 on Low $Na^+$ Diet | Normal 1-21 on High $Na^+$ Diet | Normal 2-16 on High $Na^+$ Diet |
| 45 | 120 | 1.1 | 19.0 | 4.2 | 195 | 66 | ... | ... | ... | 220 |
| 46 | 120 | ... | 22.3 | 4.3 | 260 | 81 | 54.0 | 94.0 | 113 | 330 |
| 47 | 10 | ... | 22.2 | ... | 140 | 43 | 124.0 | ... | 83 | >160 |
| 48 | 10 | 1.4 | 22.0 | 6.0 | 195 | 83 | 259.0 | ... | 195 | ... |
| 59 | 10 | 1.1 | 22.0 | 4.2 | 168 | 33 | 45.0 | ... | 86 | ... |
| 60 | 10 | ... | 22.4 | ... | 148 | 40 | 78.0 | ... | 153 | 315 |
| 61 | 10* | ... | 24.4 | ... | 144 | 48 | 114.0 | ... | 325 | 128 |
| 62 | 10* | 1.3 | 22.8 | 5.6 | 167 | 52 | 101.0 | ... | 153 | 301 |
| 122 | 120 | ... | ... | 4.3 | ... | ... | ... | ... | ... | ... |
| 123 | 120 | 0.9 | 28.3 | ... | 205 | ... | ... | ... | ... | ... |
| 124 | 120 | 0.9 | ... | 4.1 | 148 | ... | 0.6 | 1.0 | ... | 1 |
| 125 | 10 | 0.9 | ... | ... | ... | ... | ... | ... | ... | ... |
| 126 | 10 | ... | 35.6 | 4.0 | 78 | ... | ... | ... | ... | ... |
| 127 | 10 | ... | 28.5 | ... | 42 | ... | ... | ... | ... | ... |
| 128 | 10 | 0.9 | 29.7 | 3.8 | 27 | ... | 2.8 | 11.0 | ... | 25 |

*Fludrocortisone acetate, 0.1 mg, administered every 6 hours.

result of methicillin interstitial nephritis.[11] Another report suggested that trimethoprim-sulfamethoxazole therapy was the cause of hyperkalemia and metabolic acidosis in a patient with leukemia, although the renal responsiveness to aldosterone was not evaluated.[12]

Our patient presented a unique opportunity for study of the renal tubular defect of interstitial nephritis in which the patient made a spontaneous recovery. His clinical presentation was similar to previous reports of hyperkalemic neuromyopathy of Addison's disease.[4] Like those previously reported, he showed minimal subjective sensory problems with profound quadriplegia. Of interest, his electrocardiogram did not show any of the classic findings of hyperkalemia.

Our patient did not respond to high levels of endogenous aldosterone and was unresponsive to exogenously administered mineralocorticoid as is characteristic of pseudohypoaldosteronism. The patient responded appropriately to a saline and hydrocortisone infusion with rapid improvement in his clinical state and serum potassium level, indicating that the determinants of renal potassium excretion—namely, intratubular sodium concentration and tubular flow rate—were operative. It can only be speculated that the interstitial nephritis was induced by the antibiotic therapy and either caused enough diffuse damage to renal tubules that they were unable to respond to aldosterone, or the aldosterone receptor site or sodium-potassium ATPase activity in the cells was reversibly altered by the inflammatory process. Longitudinal studies of the patient showed complete resolution of his salt-losing problem.

#### REFERENCES


1. Finch CA, Sawyer CG, Flynn JM: Clinical syndrome of potassium intoxication. Am J Med 1946; 1:337-352

2. Armstrong FA: Hyperkalemic familial periodic paralysis. Ann Intern Med 1962; 57:455-461

3. Rado JP, Marosi J, Szende L, et al: Hyperkalemic changes during therapy for cirrhosis and ascites with special reference to hyperkalemic intermittent paralysis. J Am Geriatr Soc 1968; 16:874-886

4. Bell H, Hayes WL, Vosburgh J: Hyperkalemic paralysis due to adrenal insufficiency. Arch Intern Med 1965; 115:418-420

5. Donnell GN, Litman N, Roldan M: Pseudohypoadrenalcorticism. Am J Dis Child 1959; 97:813-828

6. Rabinowitz D, Rosler A, Theodor R, et al: Salt wastage, raised plasma renin activity and normal or high plasma aldosterone: A form of pseudohypoaldosteronism. Lancet 1973; 1:959-962

7. Bierich JR, Schmidt U: Tubular Na-K-ATPase deficiency the cause of the congenital renal salt-losing syndrome. Eur J Pediatr 1976; 121:81-87

8. Hadler NM, Gill JR, Gardner JD: Impaired renal tubular secretion of potassium, elevated sweat sodium chloride concentration and plasma inhibition of erythrocyte sodium outflux as complications of systemic lupus erythematosus. Arthritis Rheum 1972; 15:515-523

9. De Fronzo RA, Cooke C, Goldberg M, et al: Impaired renal tubular potassium secretion in systemic lupus erythematosus. Ann Intern Med 1977; 86:268-271

10. Rado JP, Szende L, Szucs L: Hyperkalemia unresponsive to massive doses of aldosterone and renal tubular acidosis in a patient with chronic interstitial nephritis: Clinical and experimental studies. J Med 1977; 7:481-510

11. Cogan MC, Arieff AI: Sodium wasting, acidosis and hyperkalemia induced by methicillin interstitial nephritis. Am J Med 1978; 64:500-507

12. Kaufman AM, Hellman G, Abramsom RG: Renal salt wasting and metabolic acidosis with trimethoprim-sulfamethoxazole therapy. Mt Sinai J Med (NY) 1983; 50:238-239


# Sarcoidosis and Pheochromocytoma


KEVIN M. MURRAY, MD
RICHARD F. SCHILLACI, MD
*San Diego*


THE MOST COMMON presentation of sarcoidosis is as bilateral, symmetric hilar adenopathy noted on chest x-ray films in a patient with minimal, if any, symptoms.[1,2] Pheochromocytoma, on the other hand, has been associated with a dramatic set of symptoms and signs related to catecholamine release by this often-sought but rarely found tumor.[3] We recently cared for a patient who had the classic symptoms of a pheochromocytoma as well as asymptomatic bilateral hilar adenopathy on chest x-ray film and who ultimately proved to have both disorders, an association that has been reported only rarely.[4,5] This case provides the opportunity to discuss the association between sarcoidosis and neoplasia and to examine whether this association might be causal or coincidental.


(Murray KM, Schillaci RF: Sarcoidosis and pheochromocytoma. West J Med 1987 Jun; 146:745-747)



From the Department of Internal Medicine (Pulmonary Division) and the Clinical Investigation Department, Naval Hospital, San Diego.



Presented at the 51st annual meeting of the American College of Chest Physicians, New Orleans, Oct 29, 1985. Abstract published in the ACCP Affiliate, vol 1, No. 1, 1986.


The opinions or assertions expressed herein are those of the authors and are not to be construed as official or as reflecting the views of the Navy Department or the naval service at large.


This article is considered, under the Copyright Revision Act of 1976, a "work of the United States government" and accordingly there is no copyright.



Reprint requests to LCDR K. M. Murray, MC, USNR, c/o Clinical Investigation Department, Naval Hospital, San Diego, CA 92134-5000.


## Report of a Case

A 29-year-old black male sailor went to sick bay with symptoms of an upper respiratory tract infection. On examination his blood pressure was 250/180 mm of mercury. His medical history was unremarkable, with no previous hypertension or cardiovascular disease. The family history was positive for mild essential hypertension. The patient was a former smoker. He said he did not use alcohol excessively or take drugs and was taking no medications.

On further questioning, the patient gave a one-year history of recurrent episodes of pounding in his chest, accompanied by a sensation of pulsation throughout his body and a feeling of impending doom. These episodes occurred randomly, approximately four times each month, with no relation to exertion, meals or emotions; they lasted from 10 to 30 minutes and resolved spontaneously. There was no history of headache, cutaneous flushing or other symptoms related to the attacks.

On physical examination the patient appeared well developed, well nourished and in no distress. The pulse rate was 84 beats per minute and the blood pressure was 170/122 mm of mercury. The eye examination, including funduscopic and slit-lamp studies, showed no abnormalities. The lungs were clear. On cardiac examination a grade 2/6 ejection murmur was heard at the lower left sternal border. There were no lifts, heaves or gallop sounds. Pulses were equal in all extremities. The abdomen was unremarkable, with no masses or bruits. There was no peripheral lymphadenopathy. The skin and extremities showed no abnormalities, and results of a neurologic examination were within normal limits.

A chest x-ray film (Figure 1) showed bilateral symmetric hilar adenopathy and no pulmonary parenchymal infiltrates. A serum angiotensin-converting enzyme level was 147 units (normal $< 125$). A urinary vanillylmandelic acid level was

21.6 ng per ml (normal 0.5 to 12), and urinary metanephrine level was 5.9 ng per ml (normal 0.3 to 0.9). A gallium 67 scan (Figure 2) showed increased uptake in the hilar areas. Pulmonary function tests were negative and arterial blood gas levels were normal. Skin tests, including intermediate-strength purified protein derivative (5 tuberculin units), 1:100 coccidioidin and *Candida*, were nonreactive. The electrocardiogram was normal. An abdominal computed tomographic scan (Figure 3) showed a large mass superior to the right kidney.

The patient was treated with a regimen of phenoxybenzamine hydrochloride for control of his hypertension and a laparotomy was done, at which a tumor mass measuring 6.5 by 5.5 by 4.5 cm was found replacing the right adrenal gland. There was no evidence of intra-abdominal or retroperitoneal adenopathy. The tumor histologically was typical of pheochromocytoma. In addition, it had several noncaseating granulomas containing Langhans'-type giant cells (Figure 4). Stains for acid-fast bacilli and fungi were negative.

## Discussion

The finding of noncaseating granulomas within the surgical specimen, in the presence of bilateral symmetric hilar adenopathy, a characteristic appearance on a gallium scan and an elevated serum angiotensin-converting enzyme level, establishes the diagnosis of sarcoidosis in our patient. This is the third reported case of coexistent sarcoidosis and pheochromocytoma. Histologic findings in the previously reported cases were identical to those in this case, including the granulomas found within the tumor. Grissom and co-workers reported a giant cystic pheochromocytoma weighing 2,100 grams in an asymptomatic patient.[4] At laparotomy, noncaseating granulomas were present in abdominal lymph nodes and throughout the tumor. This finding, with a chest x-ray film showing unilateral hilar adenopathy and the presence of cutaneous anergy, was felt to establish the diagnosis of systemic sarcoidosis. A gallium scan was not done. Leophonte and associates reported a pheochromocytoma in a patient with a four-year history of thoracic and cutaneous sarcoidosis.[5] Again, noncaseating granulomas were found within the tumor. In both previously reported cases of pheochromocytoma and sarcoidosis, it was concluded that the association was purely coincidental.

There have been numerous reports of patients with carcinoma who on histopathologic examination have had noncaseating granulomas in regional lymph nodes draining their tumors.[6,7] These granulomas have been thought to be a normal immunologic reaction to some tumor-related antigen or metabolite, and their presence does not appear to place a patient at higher risk for the development of systemic sarcoidosis. Of greater pertinence to our discussion are the many reports of systemic sarcoidosis in patients with malignancy. Jalan and colleagues reported the case of a patient who had adenocarcinoma of the terminal ileum in an area of "backwash ileitis" due to ulcerative colitis.[8] Lymph nodes in the ileocecal area, the mesentery and the mediastinum were positive for noncaseating granulomas. This suggests that patients with generalized sarcoidosis may have an increased tendency for localized granulomatous reactions to develop in response to neoplastic

**Figure 2.**—A gallium 67 scan shows increased uptake of $^{67}Ga$ in both hila.

**Figure 1.**—A chest x-ray film shows symmetric bilateral hilar adenopathy.

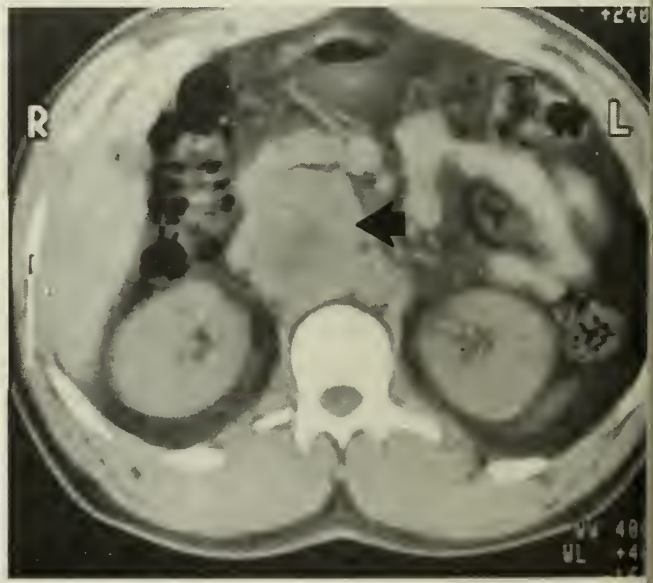



**Figure 3.**—An abdominal computed tomographic scan shows a large right adrenal mass **(arrow)**.

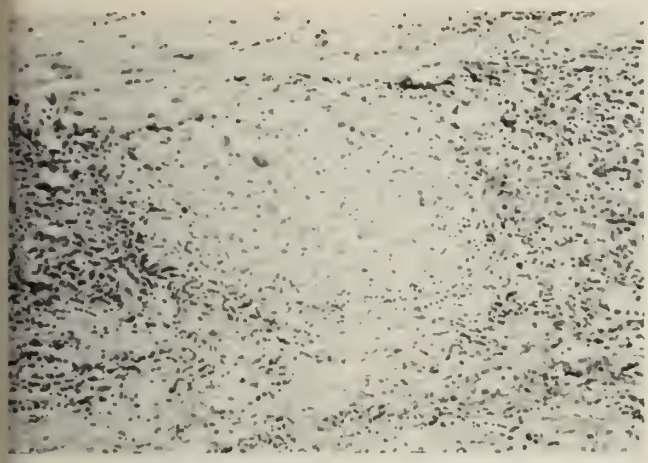


**Figure 4.**—A pathologic specimen shows noncaseating granulomas within a pheochromocytoma (original magnification × 400).

tissue. An alternative explanation, one that would also account for the findings in our patient, is that some product of the neoplastic tissue first incites the local granulomatous response and then the systemic sarcoidosis.

The possibility that sarcoidosis predisposes to malignancy must also be considered. It is known that cell-mediated immunity in sarcoidosis is abnormal.[9] An absolute lymphopenia, as well as an alteration in the T-cell helper-suppressor ratio and an impaired in vivo responsiveness of T cells to mitogens, is often found. It has been suggested that most of these changes are the result of intense granulomatous inflammation occurring throughout the body, with sequestration of helper T cells in involved tissues, leading to peripheral lymphopenia and altered in vivo responsiveness. These changes are probably responsible for the common clinical finding of cutaneous anergy but are otherwise of questionable significance. Patients with sarcoidosis, for example, are not plagued by opportunistic infections, and all immunologic abnormalities seem to resolve when the disease remits. Nonetheless, it is possible that patients with sarcoidosis have some subtle defect in cell-mediated tumor surveillance, which could lead to an increased incidence of neoplasia.

Brincker and Wilbek reviewed 2,544 cases of sarcoidosis and found 48 cases of cancer, significantly more than expected.[10] The excess was accounted for, however, by an increased number of lymphomas and bronchogenic carcinomas, both of which are well known to mimic sarcoidosis clinically. Tissue correlation was obtained in only five patients, and it is not clear that these patients had systemic sarcoidosis rather than mere local granulomatous inflammation. In another study, Brincker reviewed 1,500 cases of lymphoma and found 19 with noncaseating granulomas.[11] Five of these patients were believed to have systemic sarcoidosis, giving a prevalence of 1 in 300, clearly higher than expected. Three cases of sarcoidosis preceded the onset of lymphoma by 8 to 14 years and two followed by 5 and 17 years; it is difficult to ascribe causality to either disease. The author hypothesized that both lymphoma and sarcoidosis reflected an underlying immunologic abnormality. Other reports of sarcoidosis preceding the discovery of malignancy are rare, and the possibility of a sarcoidosis-related tumor diathesis remains conjectural.

Because there are so few data to support a causal relationship between sarcoidosis and pheochromocytoma, we examined the probability that this association was based on chance alone. The annual incidence of sarcoidosis is 11 to 19 cases per 100,000 population, and it is much more common in blacks, with an incidence in one study of 47.6 cases per 100,000 persons.[1] With a population of 200 million in the United States, we would expect 22,000 cases of sarcoidosis annually. It has been estimated that at least 10% of the adult population has hypertension, which would mean that 2,200 patients annually have both sarcoidosis and hypertension. If the incidence of pheochromocytoma is the same in these patients as in the general hypertensive population,[3] we would expect to find 0.1%, or two cases each year, of pheochromocytoma and sarcoidosis, even if no pathophysiologic association existed! While it is possible that sarcoidosis predisposes to malignancy or that uncharacterized products of neoplastic tissue lead to local granulomatous reactions and systemic sarcoidosis, the independent incidences of pheochromocytoma and sarcoidosis are such that this particular association is most likely coincidental.

#### REFERENCES

1. Mitchell DN, Scadding JG: Sarcoidosis. Am Rev Respir Dis 1974; 110:774-802

2. Katz S: Clinical presentation and natural history of sarcoidosis, *In* Fanburg B (Ed): Sarcoidosis and Other Granulomatous Diseases of the Lung. New York, Marcel Dekker, 1983, pp 203-224

3. Manger WM, Gifford RW: Pheochromocytoma. New York, Springer-Verlag, 1977

4. Grissom JR, Yamase HT, Prosser PR: Giant pheochromocytoma with sarcoidosis. South Med J 1979; 72:1605-1607

5. Leophonte P, Dutau G, Bouissou H, et al: Sarcoidose et phéochromocytome surrénalien. Poumon Coeur 1972; 28:333-337

6. Gorton G, Linnell G: Malignant tumors and sarcoid reactions in regional lymph nodes. Acta Radiol 1957; 47:381-392

7. Symmers WC: Localized tuberculoid granulomas associated with carcinoma. Am J Pathol 1951; 27:493-573

8. Jalan KN, MacLean N, Ross JM, et al: Carcinoma of the terminal ileum and sarcoidosis in a case of ulcerative colitis. Gastroenterology 1969; 56:583-588

9. Daniele RP, Dauber JH, Rossman MD: Immunologic abnormalities in sarcoidosis. Ann Intern Med 1980; 92:406-416

10. Brincker H, Wilbek E: The incidence of malignant tumors in patients with respiratory sarcoidosis. Br J Cancer 1974; 29:247-251

11. Brincker H: Sarcoid reactions and sarcoidosis in Hodgkin's disease and other malignant lymphomata. Br J Cancer 1972; 26:120-123

# Correspondence

## Management of Lumbar Disc Disease

TO THE EDITOR: Gerald G. Hirschberg, MD, in his correspondence regarding outpatient treatment of lumbar disc disease in the March issue, categorically bestows upon this nonsurgical management the property of being "entirely without risk."[1]

Motor weakness and sphincteric disturbances are well documented in patients with lumbar disc herniations, considerably more commonly preoperatively than postoperatively. Even sudden and disastrous neurological deficits occur.[2,3]

It is myopic and simplistic to state that "the end results of adequate nonsurgical management are considerably better than those of surgical management." Patients with nonsurgical lumbar disc disease do better without operations; patients with surgical lumbar disc disease are best off being operated upon.

MICHAEL H. SUKOFF, MD
*801 N Tustin Ave, Suite 406*
*Santa Ana, CA 92705*

REFERENCES

1. Hirschberg GG: Nonsurgical treatment of lumbar disc sciatica (Correspondence). West J Med 1987 Mar; 146:365
2. Garrido E, Rosenwasser RH: Painless footdrop secondary to lumbar disc herniation: Report of two cases. Neurosurgery 1981 Apr; 8:484-486
3. Wilberger JE Jr, Pang D: Syndrome of the incidental herniated lumbar disc. J Neurosurg 1983 Jul; 59:137-141

## Infection Associated With Joystick Mimicking a Spider Bite

TO THE EDITOR: We wish to focus *WJM* readers' attention on another complication associated with video games—one that originally presented as an "infected spider bite."

A 17-year-old right-handed boy noted progressive swelling and redness of his left hand seven days before admission. Two days before admission he was given penicillin intramuscularly and oral cephalexin to take at home. The swelling did not subside and the hand became very painful, so he came to the medical center for treatment. On admission his mother reported that she had seen many spiders around the house with a violin pattern on their backs, and that her son had probably been bitten by a spider. He was febrile (101.7°F)—38.7°C—and his left hand was grossly edematous and indurated with a violaceous hue. Penicillin, methicillin and gentamicin were administered intravenously. Incision and drainage of the webspace between the second and third fingers was performed with gross pus recovered. A pure culture of *Staphylococcus aureus* susceptible to methicillin and cephapirin was isolated and therapy was changed to cephapirin. After seven days of parenteral antibiotic therapy, the edema, erythema and fever had disappeared and the patient was discharged home.

Further questioning revealed that the young man was spending almost all of his time playing his favorite video game, which involved a fighting kung fu character. The patient used his left hand in manipulating a ball-shaped joystick to move the figure up, down, left and right, and his right in operating buttons to kick and jab. Extensive use of the joystick resulted in blisters on his left palm. He rubbed the blisters off, and an infection resulted that progressed to abscess formation.

Neuromuscular complications of video games ("pseudovideoma,"[1] "Pac-Man phalanx,"[2] "firing-finger syndrome"[3] and "Space Invaders wrist"[4]) have been reported, as well as video game-induced seizures,[5] but we have not come across any reports of an infectious complication of video games. Perhaps video game players should wear gloves to protect their palms, similar to ones worn by golfers and baseball players, who also need to get a firm grip on their respective sticks.

GARWIN B. SOE, MD
LARRY M. GERSTEN, MD
JEANETTE WILKINS, MD
MICHAEL J. PATZAKIS, MD
J. PAUL HARVEY, MD
*Departments of Pediatrics and Orthopedics*
*Los Angeles County-University of Southern California Medical Center*
*1129 North State St, Room 2G24*
*Los Angeles, CA 90033*

REFERENCES

1. Behr JT: Pseudovideoma (Letter). J Hand Surg (Am) 1984; 9:613-614
2. Gibofsky A: Pac-Man phalanx (Letter). Arthritis Rheum 1983; 26:120
3. Wicks I: Space invaders (Letter). Med J Aust 1981; 2:648
4. McCowan TC: Space Invaders' wrist (Letter). N Engl J Med 1981; 304:1368
5. Jeavons PM, Barton ME, Bishop A: Seizures and hand-held space invaders (Letter). Lancet 1982; 2:648

## The Elusiveness of Truth

TO THE EDITOR: Error seems to dog our lives and everything we do, but it was ever thus.

I was reading the other day the original description of Addison's disease, which in fact was called Disease of the Supra-Renal Capsules, by Dr Thomas Addison. The description was published in 1855, just a year before the California Medical Association was founded. In it he describes 11 cases of what has come to be known as Addison's disease. Curiously enough, case number eight, which was that of Elizabeth Lawrence, probably represents as perfect an example of acanthosis nigricans as one would ever hope to see. She was a short woman with gastric cancer with pronounced wasting and with metastasis to one adrenal gland but not to the other. Since functional adrenal deficiency is extremely rare even with replacement of both adrenals, the involvement of a single one makes functional adrenal insufficiency very unlikely. Add to that the marvelous drawing of the acanthotic lesions in her left axilla and in the suprasternal area, and I think one has a perfect example of a case of Addison's disease, which is not Addison's disease but in fact acanthosis nigricans complicating stomach cancer. Years ago, Henry Kaplan pointed out that at least three of the cases of Hodgkin's disease described in the original series at Guy's Hospital by Thomas Hodgkin were almost certainly not Hodgkin's disease. I believe that Dr Ronald Dorfman confirmed this fact.

I wonder how many of the things which I think are true are, in fact, in error. I wonder how many other people have discovered what appears to me to be an error, much before I did.

LAURENS P. WHITE, MD
*Clinical Professor of Medicine*
*University of California, San Francisco, School of Medicine*
*1580 Valencia St*
*San Francisco, CA 94110*

## Wright's Law

TO THE EDITOR: After 40 years of research, Edwin S. Wright, MD, has evolved a new economic theory of world-shaking importance. It is called Wright's theory of economic determinism. Its author modestly believes the theory will place him in history beside Karl Marx (theory of dialectical materialism) and Adam Smith *(Wealth of Nations)*. Probably a Nobel Prize will result.

The theory of economic determinism is elegantly simple. It says, "in any situation, the economics determine the action." A few simple examples follow.

*Example 1.* A glaucoma patient no longer responds to medication and the clinician must now choose surgical treatment. Should he or she use laser trabeculoplasty or surgical trabeculectomy? With laser treatment, reduced intraocular tension lasts 4 to 12 months and then it returns to prelaser levels. Surgical trabeculectomy is effective immediately in 95% of cases. The clinician employs Wright's theory of economic determinism and the choice is immediately clear. It is better to get paid for two operations rather than one, so the clinician does the laser treatment first and then the trabeculectomy.

*Example 2.* The green traffic light comes on and A drives through the intersection but, seeing a gorgeous girl in a mini skirt, he suddenly stops. B driving behind A can't stop in time and hits A's car, though rather lightly. A and B get out of their cars and survey the damage, which is negligible. They proceed on their way but A's wife comments on what an imbecile he is and he ought to sue. A consults his lawyer as to whether or not he was grievously damaged. They now apply Wright's law. Of course he was damaged so they sue for $250,000 and the insurance company settles for $18,000. A and his lawyer are happy by virtue of Wright's law.

*Example 3.* Government officials desire to aid the Contras but not enough money is given by Congress. How can the financial status of the Contras be improved? They apply Wright's law and at once the problem is solved. Sell arms to eager but illegal customers and divert the profits to those whom the officials believe are deserving recipients.

The three examples are only a few of the universal applications of the law. Wright modestly believes that application of his law will quickly solve most of life's problems.

E. S. WRIGHT, MD
*10614 Riverside Dr*
*North Hollywood, CA 91602*

## Dollar Mentality

TO THE EDITOR: Dollar Mentality[1] is a MAD (Medical Anonymity Disorder) caused by deficiency of DPR (the Doctor-Patient Relationship). He who pays the piper calls the tune, so those RAPS (Radiologists, Anesthesiologists, Pathologists and Surgeons) who sold their souls to the BRP (Bureaucracy, Regulators and Politicians, pronounced BuRP) in the high-pay HIC (Hospital-Insurance Complex, pronounced as in HICcup) will be the first to hear the DRG (Diagnostic-Related Group, pronounced DiRGe).

Other susceptibles include cardiologists and gastroenterologists who split fees with hospitals by doing procedures there like colonoscopy, which I do in my office on everyone over age 40, every five years, "regardless of ability to pay" (dusty motto of the Alameda-Contra Costa Medical Association). My treatment for MAD also includes the acceptance of Medi-Cal patients—but not Medi-Cal payments (which hardly cover the cost of the red tape). I won't feed its BRP and HIC.

The third symptom of this MAD is CHRN (Colleague High Referral Number, pronounced CHuRN). A patient with irritable bowel, dyspareunia, palpitations, pyorrhea and back pain may be CHRNed among five specialists more concerned with BRP, HIC and the dollar than the patient.

Treatment for MAD is DPR, referring not only to the Doctor-Patient Relationship, but also to its natural outgrowth, Doctor-Patient Responsibility (a two-way street). One cannot give health, it must be *earned.* We should contract with patients and their employers for SINE: Smokeless, Sober, Safety-belted; Interviewed, Inspected and Informed yearly, for Naturalized, Neutralized and Normalized *lifestyles*—Entrusted, Enriched and Enlivened with employer trust accounts ("Health Pay"), instead of premiums.

DPR can grow SINE now, independent of BRP, HIC and CHRN. I believe it can cure the dollar mentality and eliminate 70% of the cost. How else empower "the judgment of the person receiving care,"—Bristow's "Aim for American Medicine"?[2]

HOWARD F. LONG, MD, MPH
*363 St Mary St*
*Pleasanton, CA 94566*

REFERENCES

1. Watts MSM: Is the dollar mentality in health care healthy? (Editorial). West J Med 1987 Mar; 146:357

2. Bristow LR: The credo of an honored profession, *In* The aim of American medicine within the constraints of today's society—A forum. West J Med 1986 Aug; 145:190-191

## Cultural Change, Social Disintegration and Medicine

TO THE EDITOR: Your editorial "Health Care in a Dreamworld" in the April issue[1] articulates the growing serious loss of élan and sense of purpose in the medical profession as it sees the substance of medicine: medical diagnosis and treatment, being eroded and destabilized. Meanwhile, the institutionalization of the process, "health care" goes merrily on its way when everyone becomes the "provider" but assumes little if any responsibility for the outcome except the physician.

There is no way out of the morass, it seems to me, but to define the terms of the controversy. To persist in accepting the role of "health care provider" and negotiate with "health care insurers" is untenable. All we can provide is medical diagnosis and treatment.

To continue on under the paradigm of "health care" as our industry and business is to guarantee system failure both in cost allocation and patient satisfaction.

The results of cultural change and social disintegration are translated at end-point to health care. Social remediation costs need to be separated from medical diagnosis, treatment and medical prevention (for example, immunization). To continue to accept a role of providing "health" and be held responsible for all the resulting costs is to accept progressive cutting of money for the care of the sick and disabled as has happened with Medi-Cal. We can continue to expect a proliferation of all sorts of complex and tenuous schemes to control costs while restricting freedom of both the patient and the physician. We can ultimately expect the physician to shift responsibility to the state in order to cope: "I was just following

orders." Unless we can define the terms, we physicians will continue to be the scapegoats for the costs of serious underlying structural problems in the society under the rubric of "health care provider."

EUGENE E. BLECK, MD
*5 Laureldale Road*
*Hillsborough, CA 94010*

#### REFERENCE

1. Watts MSM: Health care in a dreamworld (Editorial). West J Med 1987 Apr; 146:471

## Importance of Dive Tables in Scuba Diving

To the Editor: As a scuba divemaster and a physician I am responding to the letters from Robert Fritz[1] and Dr Greenhouse[2] in the March 1987 issue.

I agree the case presented of meralgia paresthetica[3] is most likely due to weight belt compression, but do wish to comment on Dr Greenhouse's statement that the dives were made at sea level by a person very experienced in the sport who took all recommended precautions.

A competent and experienced diver makes every dive a no-decompression dive. The maximum time limit at 80 feet is 40 minutes. A 50-minute dive would require a 10-minute decompression stop at 10 feet, as stated by Mr Fritz.

Scuba diving is a challenging and fun sport, but also one in which life-threatening complications can occur if divers are careless in their regard for the dive tables.

SUSAN EILE, MD
*20406 Redwood Road, Suite F*
*Castro Valley, CA 94546*

#### REFERENCES

1. Fritz R: Scuba diver's thigh or the bends? (Correspondence). West J Med 1987 Mar; 146:366
2. Greenhouse AH: Scuba diver's thigh or the bends? (Correspondence). West J Med 1987 Mar; 146:366-367
3. Greenhouse AH, Page K: Scuba diver's thigh (Correspondence). West J Med 1986 Nov; 145:698-699

Topics in Primary Care Medicine

# A Clinician's Guide to Helping Patients Change Behavior

ALBERT R. MARTIN, MD, *and* THOMAS J. COATES, PhD, *San Francisco*

*"Topics in Primary Care Medicine" presents articles on common diagnostic or therapeutic problems encountered in primary care practice. Physicians interested in contributing to the series are encouraged to contact the series' editors.*

BERNARD LO, MD
STEPHEN J. McPHEE, MD
Series' Editors

Helping patients to change behavior is a challenge for all physicians practicing clinical medicine. Physicians possess great understanding of disease, but treatment and prevention frequently rely on patients' ability and willingness to implement medical and life-style changes. Adherence to a prescribed regimen of medication occurs only 50% to 70% of the time, and only 5% to 30% of patients comply with preventive measures such as quitting smoking, losing weight or changing diet. The latter figures are particularly discouraging because evidence strongly suggests that a major improvement in the health of Americans will require changes in life-style and personal habits.

Most physicians do not feel confident about motivating patients to engage in health-promoting behavior, in part because of the difficulty of the task and partly because of a lack of training in this aspect of practice. In this article we present a guide to behavior therapy with basic techniques that can be incorporated into medical practice. Rather than presenting a complete conceptual discussion of all behavioral approaches, our goal is to give specific examples of behavioral strategies that allow clinicians to be more effective.

## Behavior Therapy

"Behavior therapy" is a broad term that encompasses several different approaches to change. A brief description of one conceptual model will place subsequent suggestions in perspective.

Factors that influence behavior in patients include information about the need for change, patients' motivation to initiate new action and their ability to carry out new patterns of behavior successfully. Physicians often concentrate on presenting information to patients, and certainly that is important. Studies suggest that information presented carefully and in simple, nonthreatening language improves adherence. Information alone, however, is insufficient for producing change in most people. Physicians regularly see patients who agree that change would be desirable, but who seemingly lack the capacity or "will power" to bring it about. Therefore, motivation and ability are essential elements of change that should receive more attention from physicians.

Perceptions of their susceptibility or vulnerability to an illness, the perceived consequences of leaving the illness untreated and an evaluation of the benefits and potential risks of taking action are essential elements that determine patient motivation. Patients are also strongly influenced by "cues to action," events that affect their sense of vulnerability, such as current symptoms, disease in family members or news media information. By being aware of this, physicians can direct attention to symptoms or information that may enhance motivation. Physicians can also affect motivation through their interaction with patients. A willingness to adhere to physicians' advice is influenced by the quality of the relationship. Adherence to the recommended treatment decreases when physicians are perceived as lacking warmth, when they fail to elicit the patient's point of view or when the interaction is viewed as negative. Motivation may be improved by allowing patients to participate more actively in their care by sharing in decisions and development of strategies.

Physicians' effect on behavior may be greatest in helping motivated patients to increase their ability to change. We will give this greatest attention because one of the best predictors of future action seems to be a person's sense of his or her ability or personal efficacy. If someone does not feel capable of carrying out an action, persuasion or exhortation are unlikely to change that perception. There are a number of well-tested strategies that can increase efficacy once physician and patient agree that change needs to take place. In the following discussion we outline four general strategies for helping patients bring about a desired change, with specific examples and techniques to illustrate each strategy. Table 1 lists the strategies and the techniques that fall in each category.

Though the strategies are discussed as ways to help people bring about change, they can help to increase motivation as well. They are useful only in the context of an ongoing physician-patient relationship when the patient wants to change. They cannot be applied *to* someone but require *cooperative effort over time.* Physicians should also be realistic in their expectations. Behavior is patterned over years and is seldom changed as the result of one encounter. Patience and repetition are often prerequisites for success.

(Martin AR, Coates TJ: A clinician's guide to helping patients change behavior. West J Med 1987 Jun; 146:751-753)

From the Division of General Internal Medicine, Department of Medicine, University of California, San Francisco, School of Medicine.

Reprint requests to Albert R. Martin, MD, Division of General Internal Medicine, University of California, San Francisco, 400 Parnassus Ave, Box 0320, San Francisco, CA 94143.

TABLE 1.—*Behavioral Change Strategies*

| *Goal Setting* | *Modifying the Environment* | *Developing New Experiences* | *Incremental Change* |
|---|---|---|---|
| Specifying a goal | Stimulus control | Monitoring | Shaping |
| Contracting | Reinforcement | Rehearsal | |
| | | Paradoxical intention | |

*Goal Setting*

Setting goals is one of the time-honored strategies of behavioral therapists. Establishing measurable goals requires a patient to determine exactly what is to be accomplished. Goals also provide benchmarks for determining success. If neither physicians nor patients establish measurable goals, frustration will occur.

*Specifying a goal.* General goals (such as "controlling diabetes") are less useful than those that are specific and measurable, such as a weight loss of 20 lb, a fasting glucose level below 150 mg per dl and a glycohemoglobin concentration of 9% or less. Goals need not be restricted to treating the disease since improving function, comfort or control provides a great sense of purpose and progress for patient and physician. It is important to document the goals in the medical record to ensure that follow-up occurs at the patient's next medical visit. Vague or unmeasurable goals can lead to apparent agreement without commitment to the specific actions needed for change. If agreeing to goals seems to be difficult, it may be that the patient's understanding or commitment is limited, or that the physician's and the patient's points of view differ. That should signal a need to explore further the patient's attitudes and understanding of the problem. If there is not commitment to the same goals, exhorting the patient is less effective than providing the patient time to think about what is to be accomplished.

*Contracting.* Contracting is one way of negotiating goals, whereby a patient agrees to achieve a specific goal or behavior by a predetermined time in exchange for a reward. Contracts with monetary or other material incentives are not very practical in a physician's office, but even without a material reward, the physician's approval is an important "payment" for successful completion of a task. Breaking a larger goal, such as losing 30 lb, into a series of smaller contracts, such as 5 lb by the next visit, translates the general goal into specific action. Verbal contracts can be recorded in the medical chart with the patient watching so that they are perceived as important and followed over time.

*Modifying the Environment*

Behavioral approaches recognize the importance of creating environments that encourage change. One wants to avoid settings that are associated with unwanted behaviors and to reduce contact with substances or activities that are to be eliminated. It is much more difficult to control urges to eat "forbidden" foods or to smoke cigarettes if they are readily available.

*Stimulus control.* Stimulus control is an example of a specific technique to eliminate environmental cues that encourage unwanted behavior and to provide reinforcement of desired change. For example, when advising patients to quit smoking, it is useful for them first to monitor where and when they smoke, including the physical location, time of day, preceding activities and emotional setting. This information can then be used to develop a list of situations they should avoid when attempting to quit. For most people, situations that are known to trigger a strong urge to smoke, such as a cocktail party, alcoholic drinks and other smokers, are best avoided. Conversely, sitting in a nonsmoking area or being with friends who do not smoke provides a stimulus congruent with the goal.

*Reinforcement.* The environment can also be structured to reinforce behavior by rewarding and encouraging positive steps made by the patient. Physicians reinforce behavior powerfully with praise and approval and also by selective attention to desired behavior. Disapproving or punishing negative behavior is generally thought to be less effective than positive rewards because the former can cause defensiveness, anger or avoidance on the part of the patient.

Reinforcement may be best provided in a patient's own environment by the patient's family and friends. Physicians are generally trained to work one-on-one with patients and may forget to involve family members or friends in patient care. There is a considerable body of literature suggesting that encouragement and reinforcement from families improve significantly patients' compliance with exercise programs, medication adherence, weight loss and other treatments.

Unwanted behavior can sometimes be reinforced unintentionally by family members, unbeknownst to the physician.

A 70-year-old woman visited her physician several times with back pain. Examination and radiologic studies revealed degenerative arthritis without signs of nerve root compression or other abnormality. The physician prescribed aspirin, regular walking and Williams's flexion exercises. During subsequent visits the patient stated that there was no improvement and that she was not able to do the exercises. Discussion with the patient's daughter revealed that the patient lived alone and was quite lonely and very anxious about engaging in any new activity. When she complained of pain, the family was advising her to rest and to go back to the physician. When she understood the nature of the problem, the daughter's approach shifted from trying to protect her mother to encouraging activity and exercise. She began to call her mother daily to reinforce the physician's prescription and to encourage the patient. Over time, the patient's complaints of pain gradually diminished, and her activity increased.

With any chronic problem, discussion of goals and methods of encouraging appropriate behavior with family members can be enormously helpful to all concerned.

*Developing New Experiences*

New experiences increase people's belief in their ability to carry out new behaviors. Physicians are in a unique position to help patients plan new experiences that enhance confidence and encourage change. Behavioral change in one area may bring about changes in self-image and esteem and allow accomplishments in other aspects of a person's life. Monitoring, rehearsal and paradoxical intention are specific techniques for helping patients learn from experience.

*Monitoring.* Monitoring is one of the frequently used behavioral techniques. Self-monitoring of blood pressure, food intake, blood glucose levels, cigarettes smoked and even expiratory flow rates is a way in which patients can become more aware of events occurring in their lives. When patients monitor their progress, they can see for themselves the causes and consequences of their behavior and can take corrective action. If patients become aware that their behavior causes particular outcomes, it strengthens motivation and enhances a sense of control. Monitoring can also be used before therapy to convince the patient of the reality of the problem and to determine where change is needed. For example, instructing a diabetic patient to monitor his or her own blood glucose levels

develops awareness of the extent of the problem and the need for change.

*Rehearsal.* Rehearsal requires patients to plan and rehearse in advance exactly how they will behave in a specific situation. This is considerably more effective than simply providing verbal instructions. Rehearsing an activity ahead of time provides an opportunity to develop confidence and skill in dealing with the actual circumstance. This technique has been used very effectively, for example, in teaching patients how to deal with postoperative pain. Patients who learned what to expect after an operation and rehearsed how to use medication and other techniques to manage postoperative pain required less analgesic medication and left the hospital sooner than unrehearsed patients. Rehearsal is most effective if patients have to develop their own strategies to overcome obstacles. The physician can assume the role of an antagonist or provide problems for the patient to solve. Examples for which rehearsal can be used by physicians are role playing with a patient on how to manage a situation that involves the temptation to drink or smoke, preplanning where and how to fit medication into a busy schedule or rehearsing how to manage an asthmatic attack or an exacerbation of diabetes mellitus.

*Paradoxical intention.* This can be effective with patients who resist suggestions by either failing to follow through or deprecating advice. Generally, it is not useful to push a patient to accept a therapeutic plan. An alternative approach is to withdraw all suggestions or to prescribe that the patient continue the undesirable behavior. The latter can be done only if it presents no immediate danger to the patient. One example of this might be to tell a smoker who is undecided about quitting to continue smoking. In fact, a suggestion can be made to increase cigarette smoking and to monitor its effects on relevant symptoms such as cough, exercise capacity or taste. Paradoxical instructions are most applicable with patients whose resistance to constructive suggestions can be used to dramatize the problem.

A 60-year-old woman with nondeforming osteoarthritis of the knees and chronic pain berated the doctor at each medical visit for not doing anything to improve her pain. Trials of virtually every anti-inflammatory drug, tricyclics, physical therapy, heat, cold applications and injected steroids had been unsuccessful. In many instances the patient used the treatment only briefly and in less than the prescribed amount. Finally the physician said he could offer nothing more. He suggested that she stop all medications and treatment because they obviously were not helping. He expressed sympathy about her pain but offered no treatment. The patient herself then suggested that one of the medications had worked "a little bit" and that she would try again. At the next visit, she again complained of pain but was satisfied with her current medication.

Sometimes patients paradoxically become more involved in their own therapy and more accepting of the limits of the problem when the physician stops offering suggestions.

### *Incremental Change*

People often can accomplish in small steps what they cannot conceive of doing all at once. Although some people can simply discard long-standing habits, most will find the task so difficult that they will give up after an initial attempt and slide back to their old behavior. Incremental changes provide a way to build new experiences in small steps without too much risk and allow a practitioner to reinforce patient success in accomplishing the early tasks. This is also a way of sequentially adding both the skills and self-observation needed to achieve the overall goal. Small failures can be useful. They can be used as opportunities to identify obstacles or pitfalls and to learn how to avoid those problems in the future.

*Shaping.* Designing a therapeutic program to fit patient preferences and making incremental changes allows patients to adapt slowly to a new behavior. For example, with a patient reluctant to take medication, beginning a drug regimen using a small (and even ineffective) dose may avoid side effects and allow the patient to become used to the idea of taking the medicine.

A 49-year-old woman with hypertension had blood pressures averaging 190/110 mm of mercury. On two previous occasions side effects developed when she was taking antihypertensive medication, and she became frightened of taking them. Consequently, she had tried other approaches including salt restriction, exercise, biofeedback and relaxation exercises, none of which were successful. Home monitoring of blood pressure was used to convince her that her blood pressure was consistently elevated. A regimen of metoprolol, 25 mg daily, was then begun with her consent. At this dose it had no therapeutic effect, but no side effects. Over a period of months the dose was gradually increased to bring about blood pressure control with only mild side effects.

Patients often have more than one problem. A treatment program or even a diagnostic workup can be added incrementally with a patient's input and consent, whereas a sudden confrontation of too many changes at once may produce a negative response.

## Summary

Perhaps the greatest power of behavior therapy lies in its assumption that change is possible through awareness and learning. Dysfunctional behavior is viewed as a learned pattern that is reinforced by past experiences, attitudes, environment and personality. Knowledge is only the first step for patients to change behavior. They must commit themselves to specific goals and engage in the process of learning that creates new experiences and often new perceptions of their abilities. An incremental process allows patients to deal with their resistance to change at a more manageable pace and allows them to build on earlier successes. Changes can then be reinforced by the physician and other important people in a patient's life to encourage continued progress. Keeping the overall principles of behavior therapy in mind, a specific program can be developed that fits the needs of the patient and the problem.

### REFERENCES

Bandura A: Social Learning Theory. Englewood Cliffs, NJ, Prentice Hall, 1977

Egbert LD, Battit GE, Welch CE, et al: Reduction of postoperative pain by encouragement and instruction of patients. N Engl J Med 1964; 270:825-827

Eraker SA, Kirscht JP, Becker MH: Understanding and improving patient compliance. Ann Intern Med 1984; 100:258-268

Francis V, Korsch BM, Morris MJ: Gaps in doctor-patient communication: Patients' response to medical advice. N Engl J Med 1969; 280:535-540

Sackett DL, Snow JL: The magnitude and measurement of compliance, *In* Haynes RB, Taylor DW, Sackett DL (Eds): Compliance in Health Care. Baltimore, Johns Hopkins University Press, 1979

# Forum

# Contemporary Aims for American Medicine—1987

## A Report on a Forum

MALCOLM S. M. WATTS, MD

American medicine is enjoying unprecedented technologic success while at the same time it is undergoing unprecedented stress. And, surprising though it may be, there seems to be no real consensus or agreement, within or without the profession, about what should be the basic aim of the medical profession in today's changing social, economic, political and even technological environment. Clearly as a nation we are entering a period of social transformation that is as yet poorly understood, and just as clearly health care is in the forefront of much of the change that is taking place in the larger environment.[1] If this is true, then might there not be opportunities for the medical profession to help shape some of the change that will take place?

A forum on the "Aim of American Medicine within the Constraints of Today's Society" was conducted in *The Western Journal of Medicine* (Vols 145 and 146) to address these issues. Readers and others were invited to submit their views constructively and succinctly. This summary report presents a proposal for three contemporary aims for American medicine that are based on published and unpublished material considered in the forum. It is hoped that it will stimulate further consideration of this subject—one that is so important for the future of health care as it continues to evolve in this nation.

### Historical Background—Medical Technology and Societal Response

For most of this century a major aim of American medicine has been the development of modern medical science and technology.[2] This received enormous impetus when the public became aware of the remarkable progress in the care of the sick, injured and emotionally disturbed that occurred during World War II. It was then that the potential benefits of the new medical science and technology for better health became obvious. Subsequently, enormous sums of money were invested by the nation in biomedical research, in the training of health professionals and in the development of other resources needed to deliver this new and better care. Over time this investment produced many changes in the medical profession. Medical scientists began to replace clinicians as the teachers and role models in the clinical departments of many medical schools and they rose to positions of influence and leadership in many professional organizations. Again, over time, preoccupation with the enzyme systems of molecular biology and the biochemistry of disease began to erode and at times even displace the practicing clinician's traditional interest and concern with the needs and feelings of patients who, as always, were seeking help, solace and caring, as well as curing, from their physicians. In short, for the past 40 years the accepted aim of American medicine has been to practice the best technical medicine that is available, with the perhaps unexpected result that less attention was often paid to the human condition in patient care.[3] The consequences of both these trends have now begun to be profound.

By the 1960s it was evident that the huge investment in research had produced further progress and dramatic successes. Society then determined to make this better care accessible for all. There soon surfaced a political consensus that health care was a person's right.[4] What has turned out to be a cascade of federal legislative interventions in health care began with the enactment of the Medicare and Medicaid laws in 1965. The purpose was to ensure access to care for the elderly and the poor. By the 1970s the costs of health care began to rise and soon were to be perceived as out of control. These rapidly rising costs prevented any further large federal subsidies for health care.[5] Instead there began a series of federal legislative efforts to restrain the rising costs. These laws included experiments with PSROs, HSAs, certificates of need, ceilings on payments to physicians and hospitals, PPOs and PROs. Most recently the federal government has imposed a system of DRGs to govern Medicare payments to hospitals. In addition, it has been the policy of the federal government to actively foster competition in the health care enterprise while at the same time increasing its attempts to regulate it.[6] None of these initiatives or programs have so far reduced the cost of care, nor do they seem likely to do so. Rather, each of them has increased it. In short, they have not worked. There is ample support for the view that today's problems in health care followed sequentially on the federal legislation to extend health care benefits to its citizenry.[7]

There was another fallout from all of this. It has been suggested that as a by-product of these almost miraculous scientific and technological advances in medicine that occurred during this time, physicians began to be perceived by many of the public as an elite group with unprecedented powers over life and death. Coincidentally, this happened more or less during a time when egalitarianism was on the rise in American society, and authority of almost any kind was being questioned and even attacked in the public arena. The perception (or the reality) of physicians and the medical profession as elite did not sit well with the egalitarian movement. The honor and respect formerly enjoyed by physicians and the medical profession became significantly eroded. The times were right for public acceptance of constraints upon doctors and the medical profession.

All of the above has led to insecurity, uncertainty, confusion and even some loss of a sense of purpose or direction among physicians and the medical profession. It now seems

(Watts MSM: Contemporary aims for American medicine—1987—A report on a forum. West J Med 1987 Jun; 146:754-758)

desirable, even necessary, to rethink some of the fundamentals of what we are about.[8] The purpose of the forum was to initiate discussion on a contemporary aim for American medicine.

## Where We Are Now

Medical science and technology have made it possible to give better care to more people than at any time in history. This has raised a host of new ethical, moral and legal questions that have yet to be resolved.[2] Contemporary biomedical science tends to describe illness as a series of biochemical events. People have been taught the power of medical science and expect to see its beneficial results in the care that they receive.[9] Not surprisingly, as more and better care is given to more people the costs have continued to rise. These costs are now considered to be unacceptable to payors in both the public and private sectors.[2] And, as an ever larger share of the gross national product has been spent on health, it is generally conceded that there have not been proportional gains in the measurements of health status.[10]

What then is to be done to contain these rising costs or to reduce them? Society has decreed that a kind of ceiling has been reached in the funding for health care.[11] The payors want a cheaper product and more accountability.[6] There has been almost a stampede to reduce the amount of health care services that are delivered.[12] Should we stifle research, cut back health professions education and training, discourage health promotion and prevention? It has been noted that the longer people live, the more health services they will consume and at greater cost.[8] Should we develop consensus-derived guidelines, DRGs for example, to control costs in the treatment of illnesses? So far DRGs have not reduced costs to the Medicare program. But costs are not the only issue. The public will not be denied the benefits of evolving medical science and technology, nor will care be denied to the increasing numbers of the elderly.[6]

Just as modern medical science and new technology have had profound effects upon society as a whole, so have the responses of society in the form of social, economic and political constraints profoundly affected health care in this nation.[2] For whatever reason the health care system is not working well. The approach of making piecemeal changes has not controlled costs, rather it has increased them.[13] With each intervention, new and often costly problems have been created and the old ones generally have not been solved either.[14] Corporate America has recently joined government in seeking ways to control the rising costs of health care. Corporate America thrives on competition, advertising and marketing.[5] Corporate America's primary concern is with the "bottom line," that is, profit or loss, with the result that indigent patients are being squeezed out of the marketplace for health care. It is not clear who will pay for the care of these patients or who will support unprofitable biomedical research as the government bows out, or who will provide the funds for the costly training of the future doctors and other health professionals that will be needed. Market forces are inherently inequitable and cannot really be held accountable. The consequences can be severe for the losers.[4] And in health care the losers tend to be the weak, powerless and susceptible—that is, the children, the elderly, disabled, poor or the afflicted—and often these may be the ones who need it most.[8]

Physicians are in pain. As we learn more and more, and can perform greater and more complicated scientific wonders, we are coming under increasing criticism for our incomes and behavior, and seem to be liked and respected less all the time.[3] Sometimes it would appear that commercialism has taken us over. The "four horsemen of commercialism"—big government, big business, the insurance complex and the hospital industry—seem to threaten to render traditional medical care obsolete.[15] There are hammering attacks against physicians and the medical profession. Doctors are no longer loved.[16] A crazy quilt has been created that has degraded physicians' self-image and confidence and has removed them from their independence.[13] There is a widespread view among the profession that medicine is in very deep trouble at the present time.

## Themes From the Forum

The purpose of the forum was not simply to outline, however briefly, the historical background or where doctors now find themselves in the many professional and public arenas of health care. The waters are troubled and indeed the seas are rough. The direction and the course that will lead to better times and smoother sailing is not clear either to practicing physicians or to the leadership of the profession as a whole. A perusal of the published and unpublished material considered in this forum uncovered five themes that appeared to run through much of the discussion, and seemed to serve as a sort of consensus from which some contemporary aims for American medicine might be derived. The five themes that were identified are as follows:

1. What it means to be a physician.
2. The heart of medicine.
3. Care of the sick.
4. Health for all.
5. Balancing conflicting needs or purposes.

### *1. What It Means to Be a Physician*

Most physicians have their own concept or belief of what it means to be a physician. They may not have thought much about it since they were in medical school or even before, when they were considering medicine as a career. Many of us thought being a physician meant being available to those who need help because they are ill, and that the physician was there to do everything within reason to help. One studied and trained in medical school, and thereafter, to be able to bring the knowledge and skills of medical science and technology to bear in caring for patients and to help relieve suffering and, if possible, to restore health. To be sure, it was understood that if one worked at it, medicine would provide a good living, but financial gain was not usually the primary goal. In fact it was assumed that a certain amount of free or part pay care would be given and there was genuine satisfaction to be gained from this.

Ideally a physician is a composite of informed professional and caring human being.[17] It may be regrettable, but it is true that too often the caring has given ground to the informed professional—that is, to science and technology in patient care. But this is not all. Economics has entered into medical practice in many ways. The profession is in an undeclared war, attacked by those who are committed to "bottom line" thinking in patient care.[15] This "bottom line" thinking is now increasingly to be found in physicians' practices where costs are rising and incomes are lower. Many physicians are now perceived to be putting dollars before healing, although

the house of medicine is by no means agreed or unified on this priority.[18] In theory, charity in patient care was supposed to have been eliminated by the health care legislation of the sixties, but this has not happened. Rather the reverse, charity by physicians and hospitals has been more or less mandated as a result of cost-cutting legislation and the more or less systematic underfunding of health care for the aged and the needy that has occurred in recent years. With all of this, the profession finds itself in a struggle for survival and a need to recover its lost esteem.[19]

It was also pointed out in the forum that the medicine we have today reflects its past. What it means to be a physician contains enduring values. Medicine will move into the future by discovering how these enduring values can be realized in the new social and cultural contexts.[20] For example, ways must be found for a physician to remain a patient's advocate in circumstances where the relationship may be highly impersonal, financially unprofitable or legally threatening. These will be tasks for medical ethics. But in the meantime we will need to adapt the ancient wisdom of our profession to the present circumstances.

Society will continue to value physicians who (1) place patients' interests ahead of their convenience, (2) offer more than knowledge and skill, namely the energy and dedication to apply them in daily contact, (3) who take time to communicate their advice as well as their compassion and (4) consider how they can heal where possible, and how they can help in any case.[17] Patients expect more from physicians than they do from other health care workers. They give up more of their independence to their physicians, and sometimes sick persons resent those upon whom they have to become dependent. Yet physicians must take charge during acute problems, give support and provide reasonable options in the care of long term illness and be concerned about maximum freedom for the patient the rest of the time.[3]

Medicine is an honored profession "if you can keep it." The credo should be "Healing First—Dollars Second."[15,18] The forum suggests that this is central to what it means to be a physician.

*2. The Heart of Medicine*

The heart of medicine is surely the direct transaction between doctor and patient.[21] The heart of medicine is close to the art of medicine. Hippocrates was quoted, "the art has three factors, the disease, the patient, the physician. The physician is the servant of the art. The patient must cooperate with the physician in combatting the disease."[14] The inner reality of the art (the heart) of medicine remains the same in spite of contemporary socioeconomic influences.[21] Physicians will still need to reconcile algorithmic medicine with a love and respect for the human as a being.[9] Physicians will need to educate themselves as to the true nature of the healing transaction where usually more is involved than simply biotechnology.[11] When illness occurs people still want a physician. They want the scalpel or intervention with chemicals. But they also want attention.[9] The one essential that a doctor can give to a patient is his or her attention. There is need to strengthen a willingness to listen and give attention.[21]

The role of physician is fundamental to human society and culture. The archetypal function of doctor has always existed. It is the blending of knowledge and love, balance between mind and heart, scientific detachment and compassionate engagement in the suffering of fellow human beings.[21] One contributor quotes Barbara Berg: "dying, disease, anguish, pain, birth, hope, courage, love—these, the absolute substance of literary work are also the integral aspects of medical work."[16] Another contributor credits David Stafford-Clark for saying the role of physician is like that of a pilot, the patient is the captain of a ship who needs help at the beginning and end of the voyage and occasionally in between. The pilot has his own journey and cannot go on trips, but can help others with their ships when they need help.[3] The appropriate role for a physician is to "Be a Pilot, Not a Pirate."

*3. Care of the Sick*

It is a given that medicine is a constellation of sciences and arts aimed at diminishing, curing and preventing pain, disability and deformity, as well as postponing death.[14] Doctors of medicine are primarily concerned with care of patients, and it is good to remember that in caring for patients doctors also determine much of how this nation spends more than 10% of its gross national product.[16] Indeed there has been great pressure upon physicians to reduce costs. The refrain from the American Association of Retired Persons (AARP) is "cut the costs and keep the care."[12] Yet it is difficult for physicians or anyone else to set limits on the proper use of health care resources with little or conflicting guidance from the reigning cultural norms. Somehow it will be necessary to learn how to commit less than all available resources while maintaining the traditional goals of caring and curing.[14] Good medical care has always included cost containment as a measure of sensible medical judgment.[13] Even assuming that much of the waste in health care is eliminated, the increasing age of the population and the ever increasing costs of sophisticated science and technology will continue to produce a staggering health bill for the nation.[22,23]

Costs and quality cannot be separated in health care. Quality and outcomes of care need more study.[12] Payors want both quality and accountability.[8] One contributor notes that the quality of care can only really be measured by the outcome experienced by a patient, and that high quality in these terms may often be less expensive than lesser quality. Quality of care decisions should remain with those affected by outcome—that is, patients working with and advised by their doctors. A broader perspective on the "bottom line" is needed.[15]

There were a number of comments about how health care is or might be delivered. The aim should be to find new ways to provide high quality care at affordable prices.[12] Another contributor suggested we must let go of the past and get a firm grip on today and tomorrow, and noted that tens of millions of people do not have health insurance and suggested some form of nationwide health insurance is needed, that it could be run by the insurance industry, that the government is capable of exercising quality and cost control, and that a large competitive medical profession is capable of providing care for all the people.[13] Another suggested that there be a pluralism of ethical medical approaches to the delivery of health care, and noted that pluralism is dominant in our society, that it is basic to social tranquillity and is what gives individualism its quality.[7] Others addressed the rationing of medical care[22] and noted that this was being accomplished to the satisfaction of the populations concerned in Canada and the United Kingdom.[23] On the other hand, HMOs, PPOs and IPAs were credited with helping to preserve private practice. But there seemed to be a sense that we deserve something better than we

have,[23] and that physicians can help modify societal constraints so as to better serve patients' needs.[14]

*4. Health for All*

Better health for all was clearly a theme running through the forum. It should be a fundamental aim of American medicine to contribute to the fullest possible extent to the health of all people.[10] One contributor said the ultimate purpose is to serve the health and medical needs of all people.[4] Technology can be considered appropriate that stresses prevention of disease, seeks treatment at primary rather than secondary or tertiary levels of care, involves patients and families in both prevention and treatment, and is economical—that is, brings the greatest good to the greatest number. The health status of minorities should be brought closer to the standard of all.[10] Prevention is to be encouraged.[24] It was noted that 65% of the lives lost before the age of 65 were due to preventable causes.[10] Health education can help.[5] There should be a larger effort toward a better understanding of human behavior and the origins of disease, a more rapid flow of ideas from bench to bedside, and a better integration of the knowledge generation potential of universities with the distribution capacity of industry.[6]

And, finally, there was concern with the prevention of nuclear war,[25] and on a broader scale it was recommended that the medical profession publicly demonstrate an abiding and aggressive concern with the health, safety and welfare of society as a whole—state, nation and the world—and become a vital force for peace, disarmament and a nuclear-free world.[26]

*5. Balancing Conflicting Needs or Purposes*

Balancing conflicting indications, risks, needs and the like is nothing new for physicians. They have highly developed skills for doing this, even when there is inadequate information. They bring their science, technologic skills and usually intimate experience with the human condition to bear on problems of health and health care. Many of the problems of communities, states, nations and even the world affect health or are affected by health, and many of these problems require finding a balance among conflicting needs or purposes. Just as in clinical problems in patient care, the knowledge, skills and the human experience to be found in the disciplines of medicine can be brought to bear on many social, economic and political problems pertaining to health and health care. Indeed one may consider that organized medicine is to the body politic as a physician is to a patient.[11]

There can be no doubt that the physician's perspective on complex social and human problems can be exceedingly valuable to society. Physicians speak not only as medical experts but as sometime patients and as knowledgeable citizens and taxpayers.[11] The forum contains many examples of conflicting purposes and conflicting needs, where input from physicians and the medical profession might help to achieve a more workable balance. Examples include the role of patient advocate versus "gatekeeper" or what quality of care is purchased at what cost,[19] or, how health care costs can be justified when so many other needs of society cry out for funding[11] or the effect of competition on health care and the conflicting forces impinging upon doctors, patients and the care that is given.[5] And in a larger dimension, in what ways can the perspective of medicine contribute anything to how best to allocate monies available in the gross national product (to bombers or nuclear power or to health and education, for example),[25] or to correcting flawed economic as well as flawed health policies?[7] Or as a learned profession, should medicine try to enhance the public's insight into what can be expected from government[7] or help to instruct the public concerning the hard lessons of finitude?[14]

These are only some of the areas of conflicting needs and conflicting forces that appeared in the forum. There are many opportunities for physicians and the medical profession to use the skills of the profession to help balance conflicting needs and purposes.

## Recommended Contemporary Aims for American Medicine

A perusal of the printed and unprinted material considered in the *WJM* forum and in this report quite clearly identifies three contemporary aims for American medicine in today's more or less hostile environment. American medicine has an honorable heritage and the present problems that beset the profession are more the results of its success than of failure. The basic message is to reaffirm medicine's traditional strengths and apply them toward finding better solutions for the problems of health and health care, be they technologic, ethical, cultural, social, economic or political in nature.

The aims for American medicine drived from the forum are as follows:

1. *Take care of the sick*
   (This is the oldest and most fundamental aim of medicine and its reason for being, now and in the future. The art, the science and human caring find their highest expression in caring for the sick.)
2. *Promote health for all*
   (This is a more modern aim for medicine and it recognizes a relationship between illness in individual persons and health for all. Its dimensions extend to all the problems of population and health in the closed biosphere. The medical profession has much to contribute to better understanding of, and better solutions to, these problems.)
3. *Work within the profession and in society to find reasonable balances among conflicting needs and purposes affecting health and health care.*
   (The growing interdependence in modern society gives rise to many conflicting purposes, pressures and needs in health care and elsewhere. Physicians have training and experience in balancing conflicting needs or goals, often when there is inadequate information. Medicine has developed skills to do this that can be brought to bear.)

## How to Do It

The strength of American medicine, whether in patient care or in the social, economic or political arenas of health care, in the final analysis lies not so much in the numbers and kinds of physicians or in the kinds of social, economic or political pressures the profession can bring to bear (although these are important), as in the traditional professional perspective doctors can bring to problems, whether in patient care or in the broader dimensions of health care in our society. This perspective is based on the special skills and human values that doctors acquire through their professional studies in the disciplines of medicine and their professional experience in caring for their fellow human beings in their adver-

sities. Just as a doctor brings all this into play when acting as physician to a patient, so can the medical profession, through its leadership, bring a similar perspective into play when functioning in the role of physician to society. And it may be that, just as physicians have now begun to market their services to patients, the time has come for the profession as a whole to begin to develop and market what might be its important new role as physician to society, and become a potentially significant new force in this increasingly interdependent world where so much that is done or is not done so profoundly affects health or is affected by it.

In conclusion, the *WJM* forum seemed to call for a reaffirmation of the concern and commitment to what it means to be a physician, to the heart of medicine (which is seen to be something other than dollars), to the primacy of patients' needs in health care, to better health for all, and to use these concerns and this commitment to help find better balances among conflicting needs and purposes in health and health care. Organized medicine should try to become better recognized as an association of concerned and committed physicians who work, individually and collectively, to bring their knowledge, skills and humanity to care of the sick, better health for all, and to finding reasonable balances among conflicting indications in the social, economic and political arenas of health care, much as they are trained to do when there are conflicting indications in the care of patients.

And finally, medicine is an honorable profession, useful to patients and to society, but only the profession can keep it so.

#### REFERENCES


1. Watts MSM: A forum to discuss an important subject (Editorial). West J Med 1986 Aug; 145:235

2. Watts MSM: The aim of American medicine within the constraints of today's society. West J Med 1986 Aug; 145:181

3. White LP: Be a pilot, not a pirate, *In* The aim of American medicine within the constraints of today's society—A forum. West J Med 1986 Oct; 145:551-552

4. Myers BA: Corporate profit or public good?, *In* The aim of American medicine within the constraints of today's society—A forum. West J Med 1986 Aug; 145:189-190

5. Keltner JL: Medicine in the future, *In* The aim of American medicine within the constraints of today's society—A forum. West J Med 1986 Oct; 145:552-553

6. Moody FG: A healthy, disease-free society, *In* The aim of American medicine within the constraints of today's society—A forum. West J Med 1986 Aug; 145:184-185

7. Palmer E: Medicine's problems reflect society's, *In* The aim of American medicine within the constraints of today's society—A forum. West J Med 1987 Jan; 146:107

8. Clever LH: The measure of society's worth, *In* The aim of American medicine within the constraints of today's society—A forum. West J Med 1986 Sep; 145:400

9. Smith AL: 'Your baby' medicine, *In* The aim of American medicine within the constraints of today's society—A forum. West J Med 1986 Nov; 145:715-716

10. Mason JO: Medicine's aims, society's constraints, *In* The aim of American medicine within the constraints of today's society—A forum. West J Med 1986 Aug; 145:185-186

11. Odell RW Jr: Educate, educate, educate, *In* The aim of American medicine within the constraints of today's society—A forum. West J Med 1987 Jan; 146:107-108

12. Pollack GE: Cut the cost, keep the care, *In* The aim of American medicine within the constraints of today's society—A forum. West J Med 1986 Aug; 145:183-184

13. Rodgers DL: Patients' needs at the center, *In* The aim of American medicine within the constraints of today's society—A forum. West J Med 1986 Nov; 145:716

14. Engelhardt HT Jr: The lessons of finitude, *In* The aim of American medicine within the constraints of today's society—A forum. West J Med 1986 Aug; 145:187-188

15. Bristow LR: The credo of an honored profession, *In* The aim of American medicine within the constraints of today's society—A forum. West J Med 1986 Aug; 145:190-191

16. Fox ERW: Medicine is a humanity, *In* The aim of American medicine within the constraints of today's society—A forum. West J Med 1986 Oct; 145:553-554

17. Mosher CG: What patients expect, *In* The aim of American medicine within the constraints of today's society—A forum. West J Med 1987 Jan; 146:106

18. Scherr MS: Healing first, dollars second, *In* The aim of American medicine within the constraints of today's society—A forum. West J Med 1986 Sep; 145:402

19. Porter GA: The glass is half full, *In* The aim of American medicine within the constraints of today's society—A forum. West J Med 1986 Sep; 145:401-402

20. Jonsen AR: Ancient tenets, contemporary meaning, *In* The aim of American medicine within the constraints of today's society—A forum. West J Med 1986 Aug; 145:182-183

21. Needleman J: The essence of being a physician, *In* The aim of American medicine within the constraints of today's society—A forum. West J Med 1986 Aug; 145:185-186

22. Block MB: An issue facing our society, *In* The aim of American medicine within the constraints of today's society—A forum. West J Med 1986 Sep; 145:400-401

23. Sloane RB: Let's discuss a national health service, *In* The aim of American medicine within the constraints of today's society—A forum. West J Med 1986 Sep; 145:401

24. Petty TL: The healthiest little community in the United States, *In* The aim of American medicine within the constraints of today's society—A forum. West J Med 1986 Oct; 145:554

25. Vanstrum GS: A Nuremberg defense, *In* The aim of American medicine within the constraints of today's society—A forum. West J Med 1987 Jan; 146:106-107

26. Klutch M: Aggressive concern for society as a whole, *In* The aim of American medicine within the constraints of today's society—A forum. West J Med 1987 Jan; 146:108

# Commentary

## Fear of the Unknown

E. R. W. FOX, MD, *Coeur d'Alene, Idaho*

We humanoids, as we walk the face of the earth, are filled with fear. Right now there are two words in the English language, "nuclear" and "x-ray," that translate into that one word: "fear."

Newspapers, the radio, TV and even movies are guilty of spreading fear of these intangibles. These elements in our daily life that we can't see, smell, feel or touch are gristmill stuff for the media. Oddly, from childhood on, it is our human nature to enjoy being scared.

When Dad throws his little one up in the air, then to be safely caught, the child says, "Do it again, Daddy!" I contend the giggle comes not from being thrown in the air, but from being safely caught.

We read those scary headlines and watch those bloodcurdling horror movies because they take us to frightening heights, and then allow us to come back to the warm and cozy little world we live in.

There is an unreasonableness in so many of our fears. Mary Jones refuses a mammogram because, as she so bluntly puts it, "I don't want no x-ray on my boobs — x-rays cause cancer." Yet she smokes two packs of cigarettes a day. With her fingers she can feel the plump roundness of the cigarette, then she can see the smoke and smell the fragrance, and as she inhales she gets that indefinable nicotine surge. Surely, anything that visible, that tangible, that pleasant cannot be harmful.

In so many ways we are like Mary, mixed-up kids with the wrong priorities. In the wing of our hospital where there is a sign "Nuclear Medicine Department," it is amusing to see people slinking along on the side of the corridor farthest from that area, fearing "nuclear" contamination if they get too close. People will drive miles out of their way to avoid passing anywhere near the Hanford Nuclear Reservation.

In their ignorance they fail to realize that nuclear medicine is a magnificent tool for unlocking many mysteries of clinical medicine, helping to save lives each day. There are even groups of well-meaning physicians who will march together, preaching against all those nuclear evils, adding to the public hysteria. You have probably noticed that the original name of nuclear magnetic resonance (NMR) scanning has been quietly changed to the less terrifying magnetic resonance imaging (MRI).

It is popular today to raise our voices against the transportation and storage of hazardous wastes, which to everyone means "nuclear waste." Our mayors rise in wrath, saying, "We shall not let those nuclear trucks come through our town!" and our governors cry out, "Never will we allow those Easterners to dump their hazardous materials in our state!"

Intelligent, supposedly well-informed people ignore or choose not to accept the fact given to us by our government's Office of Technology Assessment that gasoline trucks, not nuclear waste transports, are involved in accidents that result in more deaths and damages than all the other hazardous materials accidents combined. Last year there were 225 tanker rollovers, with 88 of them resulting in fatalities. Yet we welcome those semi-trailers so that we, in turn, can fill our tanks and join the highway turmoil that claims 50,000 lives each year. To my knowledge, here in America there is no recorded death attributable to the nuclear energy industry.

Recently the press has come upon another invisible, intangible monster that is stealthily creeping up on us — radon. We are told that this deadly substance, a degradation product of plutonium, is right there in the soil beneath our homes, just waiting to seep through the cracks in the foundation. We are frightened, knowing that even within the walls of our private castles we cannot escape the threat of irradiation.

Now these fears have stalked into our kitchens. Some months ago I wrote in this journal about Maizie's problem of flatulence induced by the consumption of beans and other lentils. I made the jocular observation that some research work had demonstrated that cobalt radiation of the can of beans might reduce the production of flatus and thereby relieve Maizie's distress. At the same time, I opined that such a practice was not likely to meet with public approval. In this I was not disappointed: several readers expressed outrage at such an idiotic idea.

It comes as a happy surprise to me that the Food and Drug Administration (FDA) has recently given the go-ahead to the administration of low doses of irradiation to certain types of food in order to eliminate insects, bacteria, parasites from fruits, vegetables, pork and seafoods. The justification for the use of this method is based on the evidence that irradiation kills trichina in pork, salmonella in fish and chicken, and reduces grain spoilage.

(Fox ERW: Fear of the unknown. West J Med 1987 Jun; 146:759-760)

Dr Fox is in private practice in Coeur d'Alene and is the Special Editor for Idaho.
Reprint requests to E. R. W. Fox, MD, 1401 E Lakeshore Dr, Coeur d'Alene, ID 83814.

There has already been an outcry from opponents who fear those invisible, intangible rays, whether they be x-ray, nuclear or cobalt 60. The FDA, on the other hand, is in the unusual position of recommending the use of a dangerous and potentially lethal modality for the common good.

Somehow these sincere critics of irradiation must be convinced that many of their fears are unfounded. Perhaps they will take some comfort in knowing that food so treated does not become radioactive and that there is no documented evidence of a carcinogenic effect. They must also be told that at the present time 60% of exported wheat is spoiled before it reaches the famine-stricken areas, a tragedy preventable by irradiation.

We humanoids enjoy hazardous recreational chemicals such as cigarettes, alcohol and marijuana because we can hold them in our hand, sip them from a glass or inhale their fumes into our lungs.

Perversely, while we ignore the great good that comes to us from x-ray and nuclear energy, we live in constant fear of them. The fear of the unknown. Senseless humanoid fear.

# Use and Safety of Antimicrobial Agents During Pregnancy

ANTHONY W. CHOW, MD, FRCP(C), *and* PETER J. JEWESSON, PhD(Pharm), *Vancouver, British Columbia*

All antimicrobial drugs are potentially harmful to a fetus. Their administration during pregnancy must be limited to specific indications, and the possible risks and benefits of therapy individually assessed. Firm data on the pharmacokinetics, efficacy and optimal use of these agents during pregnancy are urgently needed. Furthermore, better understanding of the nature and consequences of various infectious processes for both a mother and fetus is necessary in order that more precise therapeutic indications for the use of these drugs during pregnancy can be developed. Available data concerning the pharmacokinetics and safety of antimicrobial agents during pregnancy have been reviewed in depth elsewhere.[1] In this communication, the salient and clinical considerations for the use of antimicrobial agents during pregnancy are summarized and recommendations regarding the use of specific antibacterial, antifungal, antiviral and antiparasitic agents against selected infections during pregnancy are outlined.

## Safety of Antimicrobial Drugs

The use of antimicrobial drugs during pregnancy poses unique concerns because of both potential toxicity and special pharmacokinetic considerations that have important therapeutic implications for both the mother and fetus.[1,2] Many antimicrobial drugs are capable of crossing the "placental barrier" of the fetoplacental unit. The teratogenic potential of many agents, however, remains unknown. Studies using animals have frequently been unreliable in predicting toxic effects in humans, and examples of false-positive and false-negative predictions are well known. The difficulty of separating potential adverse effects of drugs from the underlying disease process for which the drug was administered further complicates this issue.

There are five major periods of concern when considering antenatal and perinatal drug use: the preconception period, the organogenesis period (first trimester), the fetal development period (second and third trimester), the labor and delivery period and the breast-feeding period. Studies in animals suggest that preconception drug exposure in both male and female animals may lead to embryonic maldevelopment or intrauterine death. During the first seven days after conception, before implantation of the fertilized ovum on the uterus, it is probable that potential teratogens exert an all-or-none effect. Differentiation of the embryo (organogenesis) begins at 14 days, and it is during this period that most drug-associated congenital abnormalities are produced. For this reason, avoidance of all drugs during the first trimester where possible is recommended. Exposure to drugs during the fetal development period is associated with a much smaller risk of major birth defects because most organ systems are already well developed. Some drugs, however, such as the tetracyclines, can cause significant adverse effects (discoloration and severe dysplasia of teeth and inhibition of bone growth) when administered during the second and third trimesters.

Table 1 lists the safety and potential risks posed by selected antimicrobial drugs during the antenatal period.[3-53]

## Pharmacokinetic Considerations

When using any antimicrobial drugs during pregnancy, recognition of the various physiologic adaptations that occur with advancing gestation is essential.[38] The net results of these adaptations is that maternal antimicrobial drug concentrations tend to be 10% to 50% lower in late pregnancy and the immediate postpartum period when compared with the nonpregnant state.[1] Antimicrobials reach the fetus either by placental transfer into the fetal circulation or by achieving sufficient concentrations in the amniotic fluid.[43] Thinning of the placental membrane with advancing gestation tends to increase fetal drug concentrations. Various disease states in the mother can also alter membrane permeability and affect the transplacental transfer of drugs to the fetus.[31]

## Treating Infections During Pregnancy

Almost any infection that may be encountered in a nonpregnant person can also occur during pregnancy. Some infections may be relatively innocuous to both mother and fetus. Such is the case for cestodiasis (tapeworms) or giardiasis. Others, such as syphilis and toxoplasmosis, may seldom pose a threat to the mother but may result in a high incidence of perinatal morbidity and mortality or congenital malformations. Finally, infections such as bacteriuria and pyelonephritis pose a particular threat to both mother and fetus. The optimal management of any infection during pregnancy, therefore, requires differentiating those circumstances under which urgent antimicrobial therapy is needed from those for which therapy is best postponed until after delivery.[1,22]

Table 2 lists the first-choice and alternative antimicrobial regimens for selected infections during pregnancy. In every case, the need for treatment must be carefully weighed against the potential toxicity of the drug to be administered.

1. Chow AW, Jewesson PJ: Pharmacokinetics and safety of antimicrobial agents during pregnancy. Rev Infect Dis 1985; 7:287-313
2. Landers DV, Green JR, Sweet RL: Antibiotic use during pregnancy and the postpartum period. Clin Obstet Gynecol 1983; 26:391-406
3. AMA Division of Drugs: Antihelmintics, *In* AMA Drug Evaluations, 5th Ed. Chicago, 1983, pp 1818-1845
4. Andelman MB: Bacteriuria of pregnancy treated with a new methenamine salt (methenamine hippurate). Therapeutics 1971; 1:15-43
5. Armon PJ: Amoebiasis in pregnancy and the puerperium. Br J Obstet Gynaecol 1978; 85:264-269
6. Assael BM, Parini R, Rusconi F: Ototoxicity of aminoglycoside antibiotics in infants and children. Pediatr Infect Dis 1982; 1:357-365
7. Bennett JE: Flucytosine. Ann Intern Med 1977; 86:319-322

(Chow AW, Jewesson PJ: Use and safety of antimicrobial agents during pregnancy. West J Med 1987 Jun: 146:761-764)

From the Division of Infectious Diseases, Department of Medicine (Dr Chow), and the Division of Clinical Pharmacy, Department of Pharmacy (Dr Jewesson), G.F. Strong Research Laboratories, Vancouver General Hospital, University of British Columbia Faculty of Medicine, Vancouver.

Reprint requests to Anthony W. Chow, MD, Division of Infectious Diseases, GF Strong Research Laboratories, Vancouver General Hospital, 2733 Heather St, Vancouver, BC, Canada V5Z 1M9.

TABLE 1.—*Safety and Potential Risks of Major Categories of Antimicrobial Agents in Pregnancy*

| Antimicrobial Agents | Use in Pregnancy* | Potential Toxicity | | References |
|---|---|---|---|---|
| | | Maternal | Fetal/Neonatal | |
| **Antibacterial** | | | | |
| Aminoglycosides | Use with caution | Oto- and nephrotoxicity | Eighth-nerve toxicity | 6 |
| Cephalosporins | Considered safe | Allergic reactions | None known | 39, 52 |
| Chloramphenicol | Relatively contraindicated | Bone marrow depression; aplastic anemia | Gray syndrome | 23 |
| Clindamycin | Use with caution | Allergic reactions; pseudomembranous colitis | None known | 29, 37 |
| Erythromycin base | Considered safe | Allergic reactions | None known | 2, 37 |
| Erythromycin estolate | Relatively contraindicated | Cholestatic hepatitis | None known | 26 |
| Methenamine mandelate | Considered safe | None known | None known | 4, 14 |
| Metronidazole | Use with caution | Blood dyscrasia; neuropathy; intolerance to alcohol | No known teratogenicity in humans | 40, 36 |
| Nalidixic acid | Relatively contraindicated | Toxic psychosis, seizures | Increased intracranial pressure; papilledema; bulging fontanelles | 34 |
| Nitrofurantoin | Use with caution | Neuropathy; hemolysis (G6PD deficiency) | Hemolysis (G6PD deficiency) | 35 |
| Penicillins | Considered safe | Allergic reactions | None known | 2 |
| Sulfonamides | Use with caution | Allergic reactions | Kernicterus; hemolysis (G6PD deficiency) | 19, 53 |
| Tetracyclines | Relatively contraindicated | Hepatotoxicity; pancreatitis; renal failure | Tooth discoloration and dysplasia; inhibition of bone growth | 13, 50 |
| Trimethoprim | Relatively contraindicated | Allergic reactions | Folate antagonism; potentially teratogenic | 53 |
| **Antimycobacterial** | | | | |
| Ethambutol hydrochloride | Use with caution | Optic neuritis | None known | 8, 46 |
| Isoniazid | Use with caution | Hepatotoxicity in rapid acetylators | Possible neuropathy and seizures | 32, 33 |
| Rifampin | Use with caution | Hepatotoxicity; hypoprothrombinemia; bleeding | No known teratogenicity in humans | 11, 46 |
| **Antifungal** | | | | |
| Amphotericin B | Use with caution | Nephrotoxicity; anemia; hypokalemia; idiosyncratic reactions | No known teratogenicity; reversible azotemia and hypokalemia | 16, 27 |
| Flucytosine | Relatively contraindicated | Hepatotoxicity; marrow aplasia | Potential teratogenicity | 7, 42 |
| Griseofulvin | Relatively contraindicated | Allergic reactions; hepatotoxicity | Potential teratogenicity | 18 |
| Ketoconazole | Relatively contraindicated | Hepatitis; adrenal suppression | Safety not established | 12 |
| Miconazole nitrate | Relatively contraindicated | Hyperlipidemia; hyponatremia and thrombocytosis | Safety not established | 28 |
| **Antiviral** | | | | |
| Acyclovir sodium | Use with caution (life-threatening infections only) | Nephrotoxicity with dehydration | None known | 48 |
| Amantadine hydrochloride | Relatively contraindicated | Anxiety, hallucinations and psychosis | Potential teratogenicity | 20 |
| Vidarabine | Relatively contraindicated | Neurotoxicity with tremor and hallucinations; thrombocytopenia and leukopenia | Potential teratogenicity | 15, 20 |
| **Antiparasitic** | | | | |
| Chloroquine phosphate | Considered safe | Ototoxicity | None at recommended doses | 25, 51 |
| Iodoquinol (diiodohydroxyquin) | Use with caution | Iodine hypersensitivity | None known | 10 |
| Diloxanide furoate | Relatively contraindicated | None | Safety not established | 5, 41 |
| Emetine hydrochloride | Relatively contraindicated | Cardiotoxicity | Fetal damage | 41 |
| Furazolidone | Use with caution | Allergic reactions; monoamine oxidase inhibition; agranulocytosis; hemolysis (G6PD deficiency) | Hemolysis (G6PD deficiency) | 41 |
| Mebendazole | Relatively contraindicated | Leukopenia; abdominal pain | Potential teratogenicity | 17 |
| Niclosamide | Use with caution | None | Safety not established | 3 |
| Paromomycin sulfate | Considered safe | Gastrointestinal disturbance | None known | 41 |
| Pentamidine isethionate | Use with caution | Hypotension, hypoglycemia, blood dyscrasia | No known teratogenicity | 49 |
| Piperazine citrate | Use with caution | Allergic reactions; seizures, visual disturbance | None known | 3 |
| Praziquantel | Considered safe | Sedation, dizziness | Safety not established | 24 |
| Primaquine phosphate | Relatively contraindicated | Hemolysis (G6PD deficiency) | Hemolysis (G6PD deficiency) | 9 |
| Pyrimethamine and dapsone | Relatively contraindicated | Hemolysis; agranulocytosis | Hemolysis; methemoglobinemia | 45 |
| Pyrimethamine and sulfadoxine | Relatively contraindicated | Allergic reactions; blood dyscrasia | Potential teratogenicity | 47 |
| Quinacrine hydrochloride | Relatively contraindicated | Hemolysis; toxic psychosis; hepatotoxicity | Safety not established | 41 |
| Quinine sulfate | Use with caution (life-threatening infections only) | Cinchonism; hemolysis; renal failure | Optic nerve hypoplasia; congenital deafness | 21, 30 |
| Spiramycin | Use with caution | Allergic reactions | None known | 44 |
| Thiabendazole | Use with caution | Allergic reactions; blood dyscrasia | Safety not established | 3 |

G6PD=glucose-6-phosphate dehydrogenase

*"Considered safe" implies a lack of evidence to suggest any significant toxicity exists; "use with caution" implies that reports of maternal or fetal toxic reactions exist and use should be closely monitored; "relatively contraindicated" implies that the risk of toxicity is high and there are alternative agents that may provide a more favorable risk-benefit ratio.

8. Bobrowith ID: Ethambutol in pregnancy. Chest 1974; 66:20-24
9. Centers for Disease Control: Prevention of malaria in travelers. MMWR 1982; 31(suppl):15s-28s
10. AMA Division of Drugs: Antiprotozoal agents, *In* AMA Drug Evaluations, 5th Ed. Chicago, American Medical Association, 1983, pp 1789-1817
11. Good JT, Iseman MD, Davidson PT, et al: Tuberculosis in association with pregnancy. Am J Obstet Gynecol 1981; 140:492-498
12. Graybull JR: Summary—Potential and problems with ketoconazole. Am J Med 1983; 74 (suppl):86-90
13. Greene G: Tetracycline in pregnancy. N Engl J Med 1976; 295:512-513
14. Harris RE: Antibiotic therapy of antepartum urinary tract infections. J Int Med Res 1980; 8:40-44
15. Hintz M, Connor JD, Spector SA: Neonatal acyclovir pharmacokinetics in patients with herpes virus infections. Am J Med 1982; 73(suppl):210-214
16. Ismail MA, Lerner SA: Disseminated blastomycosis in a pregnant woman—Review of amphotericin B usage during pregnancy. Am Rev Respir Dis 1982; 126:350-353
17. Keystone JS, Murdoch JK: Mebendazole. Ann Intern Med 1979; 91:582-586
18. Klein MF, Beall JR: Griseofulvin: A teratogenic study. Science 1972; 175:1483-1484

TABLE 2.—*Recommended Antimicrobial Regimens for Selected Infections During Pregnancy*

| Clinical Setting | First Choice Regimens | | Alternative Regimens | |
|---|---|---|---|---|
| | Drug | Dose* | Drug | Dose* |
| Urinary tract infection | | | | |
| Asymptomatic bacteriuria | Ampicillin | 500 mg qid PO × 7-10 d | Nitrofurantoin | 100 mg qid PO × 7-10 d |
| | *or* Cephalexin monohydrate | 250-500 mg qid PO × 7-10 d | *or* Sulfisoxazole | 500 mg qid PO × 7-10 d |
| Cystourethritis | Ampicillin | 500 mg qid PO × 1 dose | Nitrofurantoin | 100 mg PO × 1 dose |
| | *or* Cephalexin monohydrate | 250-500 mg PO × 1 dose | *or* Sulfisoxazole | 2 grams PO × 1 dose |
| Pyelonephritis | | | | |
| Acute | Ampicillin | 2 grams every 6 h IV × 7-14 d | Gentamicin sulfate* | 3-5 mg/kg/d in 3 divided doses × 7-14 d |
| | *or* Cefazolin sodium | 1-2 grams every 8 h IV × 7-14 d | *or* Tobramycin sulfate | |
| Chronic | Nitrofurantoin | 50-100 mg at bedtime PO for duration of pregnancy | Sulfisoxazole | 500 mg bid PO for duration of pregnancy |
| *Chlamydia trachomatis* infection | Erythromycin | 500 mg qid PO × 7-14 d | Sulfisoxazole | 500 mg qid PO × 10-14 d |
| Gonorrhea | Procaine penicillin G (aqueous) | 4.8 million units IM × 1 dose | Spectinomycin HCl | 2 grams IM × 1 dose |
| | *or* Ampicillin | 3.5 grams PO × 1 dose | *or* Cefoxitin sodium | 2 grams IM × 1 dose |
| | *or* Amoxicillin trihydrate | 3 grams PO × 1 dose | *plus* Probenecid | 1 gram PO × 1 dose |
| | each with probenecid | 1 gram PO × 1 dose | | |
| Syphilis | | | | |
| Primary, secondary and latent | | | | |
| <1 year duration | Penicillin G benzathine | 2.4 million units IM × 1 dose | Erythromycin | 500 mg qid PO × 15 d |
| >1 year duration | Penicillin G benzathine | 2.4 million units IM weekly × 3 doses | Procaine penicillin G (aqueous) | 600,000 IU IM/d × 15 d |
| | | | *or* Erythromycin | 500 mg qid PO × 30 d |
| Neurosyphilis | Procaine penicillin G (aqueous) | 12-30 million units IV daily × 10 d | ... | ... |
| | followed by penicillin G benzathine | 2.4 million units IM weekly × 3 doses | | |
| | *or* Procaine penicillin G *plus* Probenecid | 2.4 million units IM/d × 10 d<br>500 mg qid PO × 10 d | | |
| | followed by penicillin G benzathine | 2.4 million units IM weekly × 3 doses | | |
| Prolonged membrane rupture or primary cesarean section | Ampicillin | 2 grams IV every 6 h × 1-2 d peripartum | Cefazolin sodium | 1 gram IV every 8 h × 1-2 d peripartum |
| Chorioamnionitis or puerperal endometritis | Ampicillin | 2 grams IV every 6-8 h × 7-14 d | Clindamycin | 600 mg IV every 8 h |
| | *or* Cefoxitin sodium | 1.5-2 grams IV every 6-8 h × 7-14 d | *plus* Gentamicin or tobramycin sulfate | 3.5 mg/kd/d in 3 doses × 7-14 d |
| | | | *or* Cefotaxime sodium | 1.5-2 grams IV every 6-8 h × 7-14 d |
| Endocarditis prophylaxis for delivery and genitourinary surgical therapy | Procaine penicillin G (aqueous) | 2 million units IM or IV 30-60 min before procedure | Vancomycin HCl | 1 gram IV slowly over 1 h, 1 h before procedure |
| | *or* Ampicillin | 2 grams IM or IV 30-60 min before proceudre | *plus* Gentamicin sulfate | 1.5 mg/kg IM or IV |
| | each with gentamicin sulfate | 1.5 mg/kg IM or IV | | |
| Tuberculosis | | | | |
| Chemoprophylaxis | Isoniazid | 300 mg/d × 6 mo | ... | ... |
| Therapy | Isoniazid | 300 mg/d PO × 9 mo<br>*or* 15 mg/kg/d PO twice a wk × 9 mo | Isoniazid<br>*plus* Rifampin | Same regimen<br>600 mg/d PO × 9 mo<br>*or* 9 mg/kg/d PO twice a wk × 9 mo |
| | *plus* Ethambutol HCl | 25 mg/kg/d PO × 2 mo *followed by* 15 mg/kg/d PO × 7 mo | | |
| Invasive mycoses† | | | | |
| Candidiasis, aspergillosis, cryptococcosis, histoplasmosis, coccidioidomycosis or blastomycosis | Amphotericin B | 0.4-0.8 mg/kg/d IV (total cumulative dose 1-3 grams) | ... | |
| Disseminated viral infections† | | | | |
| Herpes simplex | Acyclovir sodium | 30 mg/kg/d IV in 3 divided doses × 10 d | Vidarabine | 15 mg/kg/d as 12-h IV infusion × 10 d |
| Varicella | Acyclovir sodium | 500 mg/m² IV every 8 h × 7 d | Vidarabine | 10 mg/kg/d as 12/h IV infusion × 7 d |

bid=twice a day, HCl=hydrochloride, IM=intramuscularly, IV=intravenously, PO=by mouth, qid=4 times a day, tid=3 times a day

*The use of aminoglycosides should be closely monitored with serum drug concentrations.
†Life-threatening infections only

*(Continued Next Page)*

(Continued from Previous Page)

TABLE 2.—*Recommended Antimicrobial Regimens for Selected Infections During Pregnancy*

| Clinical Setting | First Choice Regimens | | Alternative Regimens | |
|---|---|---|---|---|
| | Drug | Dose* | Drug | Dose* |
| Malaria | | | | |
| Chloroquine-sensitive | | | | |
| Prophylaxis | Chloroquine phospate | 300 mg base PO weekly | ... | ... |
| Treatment | Chloroquine phosphate | 600 mg base PO, then 300 mg PO in 6 h, then 300 mg/d PO × 2 d | ... | ... |
| Chloroquine-resistant | (Primaquine phosphate should not be given until after delivery) | | | |
| Prophylaxis | No suitable agent (the use of both pyrimethamine-sulfadoxine and pyrimethamine-dapsone is contraindicated) | | ... | ... |
| Treatment | Quinine sulfate | 650 mg base PO every 8 h × 3 d | ... | ... |
| | *plus* Clindamycin | 900 mg PO tid × 3 d | ... | ... |
| Toxoplasmosis | Spiramycin | 2-4 grams PO daily × 3-4 wk | ... | |
| Pneumocystosis† | Pentamidine isethionate | 4 mg/kg/d IM × 12-14 d | Trimethoprim (TMP) and sulfamethoxazole (SMX) | 20 mg/kg/d (TMP) and 100 mg/kg/d (SMX), PO or IV in 4 doses × 14 d |
| Amebiasis | | | | |
| Symptomatic | Metronidazole | 750 mg PO tid × 5-10 d | ... | ... |
| | *plus* Iodoquinol (diiodohydroxyquin) | 650 mg PO tid × 20 d | ... | ... |
| Asymptomatic | Iodoquinol | 650 mg PO tid × 20 d | Paromomycin sulfate | 10 mg/kg PO tid × 5-10 d |
| Giardiasis | Metronidazole | 250 mg PO tid × 7 d | Paromomycin sulfate | 10 mg/kg PO tid × 5-10 d |
| Trichomoniasis | Metronidazole | 1 gram PO bid × 2 doses *or* 250 mg PO tid × 7-10 d | Clotrimazole vaginal cream | 100 mg topically at bedtime × 7 d |
| Helminthic infections | | | | |
| Ascariasis | Piperazine citrate | 4 grams PO × 1 dose | ... | ... |
| Strongyloidiasis | Thiabendazole | 25 mg/kg PO bid × 2-5 d | ... | ... |
| *Taenia solium, Taenia saginata, Diphyllobothrium latum* | Niclosamide | 2 grams PO × 1 dose | ... | ... |
| Cysticercosis | Praziquantel | 5-10 mg/kg PO × 1 dose | ... | ... |
| Hookworm, enterobiasis, trichuriasis | Delay treatment (mebendazole) until after delivery | | | |
| Trichinosis | Thiabendazole | 25 mg/kg PO bid × 5 d | ... | ... |
| Schistosomiasis | | | | |
| *Schistosoma haematobium* or *Schistosoma mansoni* | Praziquantel | 40 mg/kg PO × 1 dose | ... | ... |
| *Schistosoma japonicum* or *Schistosoma mekongi* | Praziquantel | 20 mg/kg PO tid × 1 d | ... | ... |

bid=twice a day, IM=intramuscularly, IV=intravenously, PO=by mouth, qid=4 times a day, tid=3 times a day

*The use of aminoglycosides should be closely monitored with serum drug concentrations.
†Life-threatening infections only.


19. Krauer B, Spring P, Dettli L: Zur pharmakokinetik der sulfonamide im ersten Lebensjahr. Pharmacol Clin 1968; 1:47-53
20. AMA Division of Drugs: Agents used to treat viral infections, *In* AMA Drug Evaluations, 5th Ed. Chicago, American Medical Association, 1983, pp 1451-1464
21. Lang PA, Jones CC: Acute renal failure precipitated by quinine sulfate in early pregnancy. JAMA 1964; 188:164-166
22. Ledger WJ: Antibiotics in pregnancy. Clin Obstet Gynecol 1977; 20:411-421
23. Leitman PS: Chloramphenicol and the neonate—A 1979 view. Clin Pharmacol 1979; 6:151-162
24. Leopold G, Ungenthüm W, Groll E, et al: Clinical pharmacology in normal volunteers of praziquantel, a new drug against schistosomes and cestodes. Eur J Clin Pharmacol 1978; 14:281-291
25. Matz GJ, Naunton RF: Ototoxicity of chloroquine. Arch Otolaryngol 1968; 88:50-52
26. McCormack WM, George H, Donner A, et al: Hepatotoxicity of erythromycin estolate during pregnancy. Antimicrob Agents Chemother 1977; 12:630-635
27. McCoy MJ, Ellenberg JF, Killam AP: Coccidioidomycosis complicating pregnancy. Am J Obstet Gynecol 1980; 137:739-740
28. McNellis D, McLeod M, Lawson J, et al: Treatment of vulvovaginal candidiasis in pregnancy—A comparative study. Obstet Gynecol 1977; 50:674-678
29. Mickal A, Panzer JD: The safety of lincomycin in pregnancy. Am J Obstet Gynecol 1975; 121:1071-1074
30. Miller RK: Drugs during pregnancy: A therapeutic dilemma. Ration Drug Ther 1981; 15:1-9
31. Mirkin BL: Perinatal pharmacology: Placental transfer, fetal localization and neonatal distribution of drugs. Anesthesiology 1975; 43:156-170
32. Mollering RC Jr: Special consideration of the use of antimicrobial agents during pregnancy, post partum, and in the newborn. Clin Obstet Gynecol 1979; 22:373-378
33. Monnet P, Kalb JC, Pujol M: Toxic influence of isoniazid on fetus. Lyon Medicale 1967; 218:432
34. Murray EDS: Nalidixic acid in pregnancy (Letter). Br Med J [Clin Res] 1981; 282:224
35. Perry JE, Toney JD, LeBlanc AL: Effect of nitrofurantoin on the human fetus. Texas J Reprod Biol Med 1967; 25:270-272
36. Peterson WF, Stauch JE, Ryder CD: Metronidazole in pregnancy. Am J Obstet Gynecol 1966; 94:343-349
37. Philipson A, Sabath LD, Charles D: Erythromycin and clindamycin absorption and elimination in pregnant women. Clin Pharmacol Ther 1975; 19:68-77
38. Philipson A: Pharmacokinetics of antibiotics in pregnancy and labor. Clin Pharmacokinet 1979; 4:297-309
39. Pratt WR: Allergic diseases in pregnancy and breast feeding. Ann Allergy 1981; 47:355-360
40. Rodin P, Hass G: Metronidazole and pregnancy. Br J Vener Dis 1966; 42:210-212
41. Rotblatt MD: Giardiasis and amoebiasis in pregnancy. Drug Intell Clin Pharm 1983; 17:187-188
42. Schönebeck J, Segerbrand E: *Candida albicans* septicaemia during first half of pregnancy successfully treated with 5-fluocytosine. Br Med J 1973; 4:337-338
43. Schwarz RH: Considerations of antibiotic therapy during pregnancy. Obstet Gynecol 1981; 58(suppl)95s-99s
44. Scott RJ: Toxoplasmosis. Trop Dis Bull 1978; 75:809-827
45. Segal HE, Pearlman EJ, Thiemanan W, et al: The suppression of *Plasmodium falciparum* and *Plasmodium vivax* parasitaemias by a dapsone-pyrimethamine combination. J Trop Med Hyg 1973; 76:285-290
46. Snider DE Jr, Layde PM, Johnson MW et al: Treatment of tuberculosis during pregnancy. Am Rev Respir Dis 1980; 122:65-79
47. Trussel RR, Beeley L: Prescribing in pregnancy—Infestations. Clin Obstet Gynaecol 1981; 8:333-340
48. Tucker WE: Preclinical toxicology profile of acyclovir: An overview. Am J Med 1982; 73(suppl):27-30
49. Western KA, Perera DR, Schultz MG: Pentamidine isethionate in the treatment of *Pneumocystis carinii* pneumonia. Ann Intern Med 1970; 73: 695-702
50. Wally JP, Adams RH, Combes B: Tetracycline toxicity in pregnancy. JAMA 1964; 189:357-362
51. Wolfe MS, Cordero JF: Safety of chloroquine in chemosuppression of malaria during pregnancy. Br Med J 1985; 290:1466-1467
52. Yamada N, Kido K, Uchida H, et al: Application of cephalosporins to obstetrics and gynecology: Transfer of cefazolin and cephalothin to uterine tissue. Am J Obstet Gynecol 1980; 136:1036-1040
53. Ylikorkala O, Sjöstedt E, Järvinen PA, et al: Trimethoprim-sulfonamide combination administered orally and intravaginally in the first trimester of pregnancy—Its absorption into serum and transfer to amniotic fluid. Acta Obstet Gynecol Scand 1973; 52:229-234

# Leaving a Cardiology Service Against Medical Advice—A Follow-Up Study

HERBERT N. OCHITILL, MD
RANDOLPH C. BYRD, MD
JANET GREENE
*San Francisco*

Noncompliant patient behavior is being increasingly recognized as a significant health care problem. A patient's degree of compliance appears to be influenced by a variety of factors.[1] Noncompliance involves many kinds of behavior including dropout from treatment. One form of dropout from treatment, premature departure from the hospital, is an especially dramatic disruption of health care.

Investigators have attempted to characterize the demographic and behavioral features of the patients and the clinical context of these events. For a cardiac patient, despite shortening stays in coronary care units, physicians presume that adverse outcome awaits the patient who leaves prematurely. The consequences, however, are unclear; there has been almost no follow-up study of this problem.

We recently reported on a case-control study of 32 patients who left a cardiology service against medical advice (AMA).[2] The groups were found to show significant differences on demographic, medical and behavioral variables. The AMA group experienced significantly fewer in-hospital cardiac complications such as heart failure and less severe chronic disability (New York Heart Association [NYHA] classification). The two groups, however, did not show significant differences regarding age, sex or discharge diagnosis.

For the follow-up study, we used the San Francisco General Hospital Medical Center records for both groups from the year after the index hospital admission. The groups are described in terms of age, sex, discharge diagnosis and NYHA classification at the time of the index hospital admission. Follow-up data include the number of patients and the total number of cardiac readmissions, the total of hospital days, number of AMA discharges and deaths. Between-group differences were analyzed by the Student's *t* test or by $\chi^2$ analysis.

Data were available on 20 patients in each group. A review of the data shows no significant differences in the variables tested (Table 1). As in the original investigation, age and sex did not distinguish the groups. The subset of the original AMA group described here is skewed toward the most disabled (mean score, NYHA classification, 2.3) of the original group (mean score, NYHA classification, 1.4). The subset of the controls has a score that closely approximates that of the original control group (mean score, NYHA classification, 2.0).

ABBREVIATIONS USED IN TEXT
AMA = against medical advice
NYHA = New York Heart Association

TABLE 1.—*Comparison of Base-line and Follow-up Data*

| *Characteristics* | *AMA** | *Controls* | *P Value* |
|---|---|---|---|
| Patients, number | 20 | 20 | |
| Sex, male, number | 16 | 13 | NS |
| Age, yr | 60 ± 14 | 61 ± 17 | NS |
| Discharge diagnoses, number | | | |
| Myocardial infarction | 3 | 4 | |
| Unstable angina | 2 | 2 | |
| Atypical chest pain | 3 | 4 | |
| Congestive failure | 4 | 5 | |
| Supraventricular arrhythmia | 3 | 1 | |
| Syncope | 1 | 2 | |
| Other | 4 | 2 | |
| NYHA classification (± SD) | 2.3 ± 0.08 | 2.1 ± 0.8 | NS |
| Follow-up | | | |
| Patients readmitted, number | 9 | 11 | NS |
| Readmissions, number | 19 | 20 | NS |
| Hospital time, days | 175 | 155 | NS |
| AMA discharges, number | 4 | 2 | |
| Deaths | 0 | 1 | |

NS = no significance, NYHA = New York Heart Association, SD = standard deviation

*Left hospital against medical advice.

The variables related to hospital use showed no significant difference between the groups, while there was a slightly greater number of discharges against medical advice in the AMA group. One patient in the control group died during the follow-up period.

Our data suggest that the premature departure of the AMA patients has not had a major adverse effect on the course of their cardiac illness. In some instances, an AMA slip is signed as a formality, though the staff anticipates minimal clinical risk.

Baile and co-workers obtained follow-up data on 22 of 29 patients an average of nine months after they signed out of a coronary care unit against medical advice.[3] Two patients were readmitted with symptoms of myocardial ischemia and two others died, neither a confirmed cardiac death.

Though lack of follow-up for 12 patients in each group raises doubts about the representativeness of the outcome, the descriptive data suggest that the subset of the AMA group is the most chronically disabled among the AMA patients and as disabled as the subset of control patients.

This study indicates that many of the patients leaving prematurely do so without deleterious consequences. The leave-taking should be free of recrimination and should be a time to optimize the chances for follow-up. Further work on the outcome of various health behaviors should be pursued.

(Ochitill HN, Byrd RC, Greene J: Leaving a cardiology service against medical advice—A follow-up study. West J Med 1987 Jun; 146:765)

From the Division of Cardiology and the Department of Psychiatry, San Francisco General Hospital Medical Center and the University of California, San Francisco, School of Medicine.

Reprint requests to Herbert Ochitill, MD, Department of Psychiatry, 7G 30, San Francisco General Hospital, 1001 Potrero Avenue, San Francisco, CA 94110.

REFERENCES

1. Haynes RB, Sackett DC: Compliance with Therapeutic Regimens. Baltimore, Johns Hopkins Press, 1976

2. Ochitill HN, Havassy B, Byrd RC, et al: Leaving a cardiology service against medical advice. J Chronic Dis 1985; 38:79-84

3. Baile WF, Brinker JA, Wachspress JP, et al: Signouts against medical advice from a coronary care unit. J Behav Med 1979; 2:85-91

## AUTHOR INDEX


Achen, Susan M. W., Van Nuys, Calif . . . (Jun) 695
Alper, Philip R., Burlingame, Calif . . . (Apr) 488
Altman, David F., San Francisco . . . (Jan) 101
Anderle, Dorothy, Encino, Calif . . . (Apr) 431
Atkinson, Joseph H., San Diego . . . (May) 615
Avasthi, Pratap S., Albuquerque . . . (May) 571

Bailie, Ira E., Turlock, Calif . . . (Apr) 488
Baker, Lori, San Diego . . . (May) 585
Baraff, Larry J., Los Angeles . . . (May) 576
Barnett, Jeffrey B., Victoria, British Columbia . . . (May) 580
Barnett, Paul G., Salinas, Calif . . . (Apr) 488
Barr, C. Hilyard, La Canada, Calif . . . (Feb) 233
Baughman, Fred A., Jr, El Cajon, Calif . . . (Feb) 236
Benecke, James E., Jr, Los Angeles . . . (Jan) 99
Bennett, Richard W., Salt Lake City . . . (Mar) 359
Bennetts, Geni A., Orange, Calif . . . (Feb) 179
Benson, D. Frank, Los Angeles . . . (Jun) 705
Bergman, Abraham B., Seattle . . . (Feb) 243
Berman, Henry S., Spokane, Wash . . . (Jun) 697
Bessman, Alice N., Los Angeles . . . (Apr) 431
Bidder, T. George, Sepulveda, Calif . . . (Jun) 695
Bleck, Eugene E., Hillsborough, Calif . . . (Jun) 749
Bleich, Howard L., Boston . . . (Feb) 236, (Mar) 366
Boylen, C. Thomas, Los Angeles . . . (Mar) 363
Brasel, Jo Anne, Torrance, Calif . . . (Apr) 476
Braveman, Paula, San Francisco . . . (Apr) 490
Brendler, Sarah J., Portland . . . (Jan) 103
Brigden, Malcolm L., Victoria, British Columbia . . . (May) 580
Bristow, Michael R., Salt Lake City . . . (May) 627
Brown, Deborah Harper, Chicago . . . (Jan) 43
Brubaker, Daniel B., Torrance, Calif . . . (May) 620
Burton, Nelson A., Salt Lake City . . . (May) 627
Byrd, Randolph C., San Francisco . . . (Jun) 765

Cagliero, Enrico, San Diego . . . (May) 614
Cairo, Mitchell S., Orange, Calif . . . (Feb) 179
Campbell, John R., Portland . . . (May) 612
Cancilla, P. A., Los Angeles . . . (Jan) 102
Caprye-Boos, Hope, Spokane, Wash . . . (Jun) 697
Carlson, James R., Davis, Calif . . . (Apr) 439
Chapman, Susan A., San Francisco . . . (Mar) 368
Chow, Anthony W., Vancouver, BC . . . (Jun) 761
Clark, Gregory L., Los Angeles . . . (Jan) 68
Clarkin, John, New York . . . (Jan) 109
Coates, Thomas J., San Francisco . . . (Feb) 234, (Jun) 751
Cohen, Richard M., Sacramento, Calif . . . (Apr) 487
Cole, B. Sharon, Seattle . . . (May) 622
Conant, Marcus, San Francisco . . . (Feb) 234
Corrie, Douglas, San Antonio, Tex . . . (May) 623
Crawley, La Vera M., San Francisco . . . (Apr) 499
Cremin, James H., Los Angeles . . . (Mar) 378
Cummings, Jeffrey L., Los Angeles . . . (Jan) 46, (Jun) 705
Cummings, Kathryn L., San Diego . . . (May) 615
Cummings, Michael A., San Diego . . . (May) 615

Davee, Thomas, San Diego . . . (Apr) 479
Davidson, Robert C., Sacramento, Calif . . . (Jan) 115
Davidson, Terence M., San Diego . . . (Apr) 434
Dela Cruz, Francine, Chicago . . . (Jan) 43
Derby, Patricia, Sepulveda, Calif . . . (Jun) 695
Desmond, Susan, San Francisco . . . (Jan) 73, (May) 621
Donald, Paul J., Sacramento, Calif . . . (Feb) 249
Doud, Robert B., San Pablo, Calif . . . (Mar) 361
Dreslinski, Gerald R., Princeton, NJ . . . (May) 622
Drumheller, Glenn W., Everett, Wash . . . (Apr) 487
Ducey, Diane E., San Francisco . . . (Jan) 39
Dugowson, Carin E., Seattle . . . (Apr) 494
Durie, Brian G. M., Tucson . . . (Mar) 322

Easton, J. Donald, Providence, RI . . . (Apr) 474
Egan, James, San Francisco . . . (May) 598
Eile, Susan, Castro Valley, Calif . . . (Jun) 750
Elvebakk, Ranveig, Davis, Calif . . . (Apr) 439
Epstein, Leon J., San Francisco . . . (Jun) 740
Erb, Blair, San Francisco . . . (Jan) 91

Fagin, James A., Los Angeles . . . (Mar) 328
Field, Stephen K., Calgary, Alberta . . . (Apr) 481
Fierer, Joshua, San Diego . . . (Apr) 479
Filloux, Francis M., Salt Lake City . . . (Feb) 207, (May) 622
Fink, Robert A., Berkeley, Calif . . . (Jan) 102
Fitzgerald, Faith T., Sacramento, Calif . . . (Mar) 316
Flynn, Neil M., Davis, Calif . . . (Apr) 439
Forsyth, Claire E., Pocatello, Idaho . . . (Feb) 236
Fox, E. R. W., Coeur d'Alene, Idaho . . . (Jan) 118, (Jun) 759
Frances, Allen, New York . . . (Jan) 109
Franklin, Cory, Chicago . . . (Jan) 43
Frawley, P. Joseph, Santa Barbara, Calif . . . (May) 620
Freeman, Gregory L., San Antonio, Tex . . . (May) 596
Fritz, Robert, San Mateo, Calif . . . (Mar) 366

Gamsu, Gordon, San Francisco . . . (Mar) 358
Ganiats, Theodore G., La Jolla, Calif . . . (Apr) 486
Garewal, Harinder S., Tucson . . . (Mar) 322
Gay, William A., Jr, Salt Lake City . . . (May) 627
Geffner, Mitchell E., Los Angeles . . . (Mar) 337
Gerbert, Barbara, San Francisco . . . (Mar) 368
Gersten, Larry M., Los Angeles . . . (Jun) 748
Gilbert, Robert P., Pocatello, Idaho . . . (Feb) 236
Gonzalez-Lee, Teresa, La Jolla, Calif . . . (Apr) 502
Grant, Igor, San Diego . . . (May) 615
Grant, J. Gary, Pacific Grove, Calif . . . (Mar) 365
Greenberg, Charles S., Sepulveda, Calif . . . (Jun) 742
Greene, Janet, San Francisco . . . (Jun) 765
Greenhouse, Arnold H., Reno, Nev . . . (Mar) 366
Grendell, James H., San Francisco . . . (May) 598

Haddox, Victor G., Sepulveda, Calif . . . (Jun) 695
Harper, Scott D., Davis, Calif . . . (Apr) 439
Harrington, William, San Francisco . . . (Jan) 91
Hart, Robert G., San Antonio, Tex . . . (May) 596
Harvey, J. Paul, Los Angeles . . . (Jun) 748
Haskell, William L., Stanford, Calif . . . (Feb) 223
Havlir, Diane V., San Francisco . . . (May) 618
Hayes, David M., Missoula, Mont . . . (Jan) 99
Hegman, Greg, Pocatello, Idaho . . . (Feb) 236
Hirschberg, Gerald G., El Cerrito, Calif . . . (Mar) 365
Hodges, Ernest J., San Francisco . . . (Mar) 361
Hoffman, Jerome R., Los Angeles . . . (Feb) 188, (May) 576
Holland, Stephen K., Lexington, Mass . . . (Apr) 494
Hollander, Harry, San Francisco . . . (Feb) 237
Houston, Mark C., Nashville, Tenn . . . (Jun) 701
Hryhorczuk, Daniel O., Chicago . . . (Jan) 43
Hull, Harry F., Sante Fe, NM . . . (Apr) 497
Hunt, Marjorie M., San Francisco . . . (Jan) 39

Iserson, Kenneth V., Tucson . . . (Mar) 331
Isman, Robert, Sacramento, Calif . . . (May) 631

Jacobs, Robert D., San Diego . . . (Apr) 434
Jalowayski, Alfredo, San Diego . . . (Apr) 434
Jewesson, Peter J., Vancouver, BC . . . (Jun) 761
Jones, Kent W., Salt Lake City . . . (May) 627
Joseph, Samuel G., Washington, DC . . . (Feb) 230

Kagan, Bruce L., Los Angeles . . . (Feb) 234
Kagnoff, Martin F., La Jolla, Calif . . . (Jan) 57
Kanel, Gary C., Downey, Calif . . . (Apr) 482
Karawande, S. V., Salt Lake City . . . (May) 627
Katz, Jacob, Orange, Calif . . . (Feb) 179
Keh, Benjamin, Berkeley, Calif . . . (Feb) 192
Kennell, Todd, Tucson . . . (Feb) 241
Kingsley, Edwin C., Las Vegas . . . (Mar) 322
Kirkpatrick, John N., Seattle . . . (Jan) 52
Kizer, Kenneth W., Sacramento, Calif . . . (May) 631
Klatt, Edward C., Los Angeles . . . (Mar) 363
Klein, Alan H., Los Angeles . . . (Apr) 476
Klontz, Karl C., Tallahassee, Fla . . . (Feb) 195
Klutch, Murray, Berkeley, Calif . . . (Jan) 108
Korula, Jacob, Downey, Calif . . . (Apr) 482
Kotler, Donald P., New York . . . (Jan) 86
Kraemer, Michael J., Seattle . . . (Jun) 697
Kraus, Jess F., Sacramento, Calif . . . (Mar) 374
Kroenke, Kurt, San Antonio, Tex . . . (May) 623
Kurahashi, Nancy, Los Altos, Calif . . . (Apr) 489

Lane, Robert S., Berkeley, Calif . . . (Feb) 192
Langer, Glenn A., Los Angeles . . . (Jun) 713
La Puma, John, Chicago . . . (May) 633
Lasnover, Alan L., Cupertino, Calif . . . (Jan) 100
Lavelle-Jones, M., San Diego . . . (May) 585
Leikin, Jerrold B., Chicago . . . (Jan) 43
Leonard, Stephen D., Tempe, Ariz . . . (Feb) 235

Levy, Jonathan M., Scottsdale, Ariz . . . (Feb) 241
Liew, Choong T., Downey, Calif . . . (Apr) 482
Lindberg, Jill, Fort Sam Houston, Tex . . . (Jan) 39
Lippe, Barbara M., Los Angeles . . . (Mar) 337
Long, Carlin S., San Francisco . . . (Mar) 344
Long, Howard F., Pleasanton, Calif . . . (Jun) 749
Lorenzi, Mara, San Diego . . . (May) 614

McBratney, R. T., Santa Cruz, Calif . . . (Mar) 367
McKusick, Leon, San Francisco . . . (Feb) 234
McNally, Edward M., La Jolla, Calif . . . (Feb) 226
McPhee, Stephen J., San Francisco . . . (Jan) 91
Mahler, Michael E., Los Angeles . . . (Jun) 705
Martin, Albert R., San Francisco . . . (Jun) 751
Melmed, Shlomo, Los Angeles . . . (Mar) 328
Meyerowitz, Basil R., San Mateo, Calif . . . (Jan) 101
Midtling, John E., Salinas, Calif . . . (Apr) 488
Miller, Bruce L., Los Angeles . . . (Jan) 46
Mills, John, San Francisco . . . (Jan) 96
Mohr, John J., Boise, Idaho . . . (Apr) 489
Montoya, Roberto, Sacramento, Calif . . . (Jan) 115
Mooradian, Arshag D., Sepulveda, Calif . . . (Jun) 742
Moossa, A. R., San Diego . . . (May) 585
Morey, Mitch K., San Diego . . . (Apr) 479
Mosher, Carter G., Sacramento, Calif . . . (Jan) 106
Mueller, Beth A., Seattle . . . (Feb) 243
Murphy, Claire, San Diego . . . (Apr) 434
Murray, Kevin M., San Diego . . . (Jun) 745
Myhre, Byron A., Torrance, Calif (Feb) 233, (Mar) 365, 378 (May) 620

Nespeca, Mark P., Salt Lake City . . . (May) 589
Newman, Nancy M., San Francisco . . . (Jan) 99
Noguchi, Thomas, Los Angeles . . . (Mar) 363
Norcross, William A., La Jolla, Calif . . . (Apr) 486
Nuttall, Frank Q., Sepulveda, Calif . . . (Jun) 742

Ochitill, Herbert N., San Francisco . . . (Jun) 765
Odell, R. W., Jr, Oakland, Calif . . . (Jan) 107

Palmer, Edward, Lake Oswego, Ore . . . (Jan) 107
Parke, Ann L., Farmington, Conn . . . (Apr) 505
Patzakis, Michael J., Los Angeles . . . (Jun) 748
Pérez-Stable, Eliseo J., San Francisco . . . (Feb) 213
Perry, Samuel, New York . . . (Jan) 109
Peters, Robert L., Downey, Calif . . . (Apr) 482
Peterson, Glen N., Oakland, Calif . . . (Jan) 101
Phelps, James R., Reno, Nev . . . (Feb) 200
Pine, Jeffrey S., Sante Fe, NM . . . (Apr) 497
Pollack, Ronald D., Northridge, Calif . . . (Mar) 381
Pollet, Stephen M., Davis, Calif . . . (Apr) 439
Poon, Man-Chiu, Calgary, Alberta . . . (Apr) 481
Powell, Malcolm M., San Francisco . . . (Jan) 39
Priver, David M., San Diego . . . (Jan) 100

Ranney, Helen M., La Jolla, Calif . . . (Apr) 473
Rapaport, Mark H., San Diego . . . (May) 615
Reeter, Alan K., Tucson . . . (Mar) 313
Regan, John J., Jr, Sepulveda, Calif . . . (Jun) 742
Renlund, Dale G., Salt Lake City . . . (May) 627
Reynolds, W. A., Missoula, Mont . . . (Apr) 486
Rivara, Frederick P., Seattle . . . (Feb) 243
Robertson, William O., Seattle . . . (Apr) 487
Rockett, Melissa, New York . . . (Apr) 431
Rodgers, Vance D., La Mesa, Calif . . . (Jan) 57
Rosenblatt, Roger A., Seattle . . . (Feb) 246
Rossetto, Bennie J., Kalispell, Mont . . . (Jan) 102
Rothrock, John F., San Diego . . . (Apr) 452
Ruvalcaba, R.H.A., Buckley, Wash . . . (Feb) 228

Sande, Merle, San Francisco . . . (May) 618
Sargent, Edward C., Eugene, Ore . . . (Mar) 367
Schaaf, Virginia Maylo, San Francisco . . . (Jan) 96
Schaller, Donald F., Phoenix . . . (Jan) 99
Scharschmidt, Bruce F., San Francisco . . . (Jun) 724
Schelbert, Heinrich R., Los Angeles . . . (Jun) 713
Schiffman, Susan S., Durham, NC . . . (Apr) 471
Schillaci, Richard F., San Diego . . . (Jun) 745
Schneiderman, Henry, Farmington, Conn . . . (Apr) 505
Schroeder, Steven A., San Francisco . . . (Mar) 368
Scott, Susan M., Albuquerque . . . (Apr) 476
Sewell, C. Mack, Sante Fe, NM . . . (Apr) 497
Shachter, Sherry P., Alameda, Calif . . . (Feb) 192
Sharer, Leroy R., Newark, NJ . . . (Jan) 88
Sharma, Om P., Los Angeles . . . (Mar) 363
Showstack, Jonathan A., San Francisco . . . (Mar) 368
Simon, Harold J., La Jolla, Calif . . . (Apr) 502
Simon, Robert R., Los Angeles . . . (May) 576
Simonson, Jay, San Francisco . . . (Jan) 96
Smith, Marc, Los Angeles . . . (May) 576
Soe, Garwin B., Los Angeles . . . (Jun) 748
Soeldner, J. Stuart, Boston . . . (Mar) 356
Sommer, Michael A., San Jose, Calif . . . (Jan) 100
Staker, Larry V., Salt Lake City . . . (Mar) 359
Staley, Nancy, Sepulveda, Calif . . . (Jun) 742
Stegman, Cary J., Scottsdale, Ariz . . . (Feb) 241
Stein, Mark G., San Francisco . . . (Mar) 358
Stevenson, Lynne Warner, Los Angeles . . . (Feb) 188
Strom, Glenn, Los Angeles . . . (May) 576
Stulbarg, Michael S., San Francisco . . . (Mar) 358
Sukoff, Michael H., Santa Ana, Calif . . . (Jun) 748

Tager, Ira B., San Francisco . . . (Apr) 461
Teret, Stephen P., Sacramento, Calif . . . (Mar) 374
Thorburn, Kim Marie, Honolulu . . . (May) 638
Tolle, Susan W., Portland . . . (Jan) 103
Tolone, Frank S., Phoenix . . . (Jan) 100
Toomey, Kathleen E., San Francisco . . . (Apr) 490
Townsend, Jeannette J., Salt Lake City . . . (Feb) 207, (May) 589, 622
Turner, Stephen, San Francisco . . . (Mar) 361
Tzamaloukas, Antonios H., Albuquerque . . . (May) 571, 620

Ukkestad, Susie, Torrance, Calif . . . (May) 620
Underhill, Lisa H., Boston . . . (Feb) 236, (Mar) 366

Van Horne, James R., Davis, Calif . . . (Apr) 439
Vanstrum, Glenn S., Del Mar, Calif . . . (Jan) 106
Veille, J. C., Cleveland . . . (Feb) 224
Velasco, Antonio R., Salinas, Calif . . . (Apr) 488
Vinters, Harry V., Los Angeles . . . (Jan) 68

Wade, Charles E., San Francisco . . . (Jan) 39
Waldron, Lester E., Sepulveda, Calif . . . (Jun) 695
Wallerstein, Ralph O., Jr, San Francisco . . . (Apr) 443
Walter, Barbara N., Orange, Calif . . . (Feb) 179
Watts, Malcolm S. M., San Francisco . . (Jan) 86, (Feb) 223, (Mar) 356, 357, (Apr) 471, 475, (May) 612, 613, (Jun) 740, 754
Webb, W. Richard, San Francisco . . . (Mar) 358
Weiss, James N., Los Angeles . . . (Jun) 713
White, Laurens P., San Francisco . . . (Jun) 748
Whiteside-Yim, Connie, Sacramento, Calif . . . (Mar) 316
Wilkins, Jeanette, Los Angeles . . . (Jun) 748
Wintemute, Garen J., Sacramento, Calif . . . (Mar) 374
Witt, Mallory D., San Francisco . . . (May) 618
Wolfstein, Ralph S., Panorama City, Calif . . . (May) 621
Wright, Craig L., Seattle . . . (Feb) 246
Wright, E. S., North Hollywood, Calif . . . (Jun) 749

Yee, Andrew, Los Angeles . . . (Mar) 363
Yoshida, S., Torrance, Calif . . . (Feb) 233
Young, Stephen G., San Francisco . . . (Apr) 479

Zelicoff, Alan Paul, Albuquerque . . . (Jan) 101

## IN MEMORIAM

*California Medical Association:*

Abbott, Dee L., Jan 19, 1987 . . . (Apr) 513
Amano, Fumiko Y., Jan 8, 1987 . . . (Jun) 780
Ash, Donald W., Apr 7, 1987 . . . (Jun) 780
Baker, Donald Duane, Jan 12, 1987 . . . (Apr) 513
Beaver, Meredith G., Jan 11, 1987 . . . (Apr) 513
Berkery, Emmet M., Nov 8, 1986 . . . (Mar) 387
Berkove, Sadie Volovick, Jan 23, 1987 . . . (Jun) 780
Best, Elbridge J., Dec 12, 1986 . . . (Mar) 387
Bjornson, Lyall A., Mar 3, 1987 . . . (Jun) 780
Bobbitt, James R., Oct 12, 1986 . . . (Apr) 513
Broadley, Paul H., Nov 9, 1986 . . . (Mar) 387
Butler, Francis H., Dec 11, 1986 . . . (Apr) 513
Calvin, George, Mar 13, 1987 . . . (Jun) 780
Carlson, Carl O., Mar 20, 1987 . . . (Jun) 780
Carroll, Vincent P., Dec 2, 1986 . . . (Apr) 513
Cavelti, Philip A., Dec 29, 1986 . . . (Apr) 513
Cherry, Clifford B., Dec 8, 1986 . . . (Mar) 387
Crary, Gerald C., Dec 9, 1986 . . . (Mar) 387
Devine, Sherman S., Aug 26, 1986 . . . (Feb) 164
Dickson, James D., Jan 1987 . . . (Jun) 780
Dodson, Jerry G., Feb 15, 1987 . . . (Jun) 780
Dowling, William F., Jul 29, 1986 . . . (Feb) 164
Dozier, David F., Sr, Sep 16, 1986 . . . (Feb) 164

Evans, Leland M., Sep 29, 1986 . . . . . (Feb) 164
Feldman, Jacob F., Nov 15, 1986 . . . . . (Mar) 387
Fields, Jack, Feb 2, 1987 . . . . . (Jun) 780
Fillmore, John R., Dec 31, 1986 . . . . . (Apr) 513
Fishman, Harvey C., Sep 27, 1986 . . . . . (Mar) 387
Flanders, Jackson, Jul 14, 1986 . . . . . (Feb) 164
Foster, Paul D., Jan 10, 1987 . . . . . (Apr) 513
Funk, John W., Mar 13, 1987 . . . . . (Jun) 780
Gaede, Menno S., Feb 8, 1987 . . . . . (Jun) 780
Gibson, Thomas E., Dec 26, 1986 . . . . . (Apr) 513
Gifford, Byron L., Sep 27, 1986 . . . . . (Feb) 164
Gilman, Philip K., Sep 25, 1986 . . . . . (Feb) 164
Gronhovd, John W., Mar 15, 1987 . . . . . (Jun) 780
Hackley, Roger W., Apr 3, 1987 . . . . . (Jun) 780
Hamblin, Merriman, Jan 29, 1987 . . . . . (Apr) 513
Harmon, Ellis D., Feb 9, 1987 . . . . . (Jun) 780
Harvey, Bernard J., Mar 27, 1987 . . . . . (Jun) 780
Heppner, Myer J., Oct 6, 1986 . . . . . (Apr) 513
Hickman, Kyrmel L., Jan 22, 1987 . . . . . (Jun) 780
Hines, Phillip Roger, Mar 16, 1987 . . . . . (Jun) 780
Holdsworth, Mode J., Oct 27, 1986 . . . . . (Mar) 387
Hume, Portia Bell, Aug 2, 1986 . . . . . (Feb) 164
Jackson, B. Richard, Dec 25, 1986 . . . . . (Apr) 513
Jackson, Leta B., Nov 27, 1986 . . . . . (Jun) 780
Jakes, Wayne Elliot, Jul 31, 1986 . . . . . (Feb) 164
Johnson, Neill P., Dec 10, 1986 . . . . . (Apr) 513
Johnson, Russell I., Oct 21, 1986 . . . . . (Apr) 513
Jones, William G. A., Dec 24, 1986 . . . . . (Apr) 513
Kastner, Scott M., Aug 23, 1986 . . . . . (Feb) 164
Kennedy, Charles R., Oct 28, 1986 . . . . . (Mar) 387
Kessler, Ernest E., Aug 23, 1986 . . . . . (Feb) 164
Kesterson, Robert L., Mar 26, 1987 . . . . . (Jun) 780
Kimball, Lloyd O., Jan 8, 1987 . . . . . (Apr) 513
King, Louise S., Dec 30, 1986 . . . . . (Apr) 513
Lawler, William H., Sr, Nov 23, 1986 . . . . . (Mar) 387
Lee, Henry Yen, Oct 28, 1986 . . . . . (Apr) 513
Leonard, Nobel D., Dec 17, 1986 . . . . . (Jun) 780
Levin, Sidney, Mar 18, 1987 . . . . . (Jun) 780
Lindner, Harold H., Jul 27, 1986 . . . . . (Feb) 164
Longley, James E., Dec 11, 1986 . . . . . (Apr) 513
Louie, Stanley, Mar 24, 1987 . . . . . (Jun) 780
Lukens, James T., Mar 12, 1987 . . . . . (Jun) 780
Lyons, Dorothy J., Sep 19, 1986 . . . . . (Feb) 164
MacCallum, Daniel B., Nov 12, 1986 . . . . . (Mar) 387
McCauley, John J., Jul 4, 1986 . . . . . (Feb) 164
McKeehan, Harold L., Sep 2, 1986 . . . . . (Feb) 164
McLin, Edward D., Dec 24, 1986 . . . . . (Apr) 513
McNaught, Robert C., Dec 29, 1986 . . . . . (Apr) 513
McReynolds, Chester C., Nov 26, 1986 . . . . . (Apr) 513
Maher, Frank M., Feb 25, 1987 . . . . . (Jun) 780
Malis, Solomon, Nov 22, 1986 . . . . . (Apr) 513
Marchesi, John C., Dec 16, 1986 . . . . . (Apr) 532
Martel, Julius, Mar 13, 1987 . . . . . (Jun) 796
Mastellos, Christopher, Dec 13, 1986 . . . . . (Apr) 532
Messenger, Harold M., Sep 3, 1986 . . . . . (Feb) 164
Mills, William, Mar 9, 1987 . . . . . (Jun) 796
Mitchell, Allen C., Mar 7, 1987 . . . . . (Jun) 796
Morris, Kathleen G., Oct 26, 1986 . . . . . (Feb) 164
Nelson, Clarence E., Dec 22, 1986 . . . . . (Apr) 532
Nesselbush, Orval P., Sep 4, 1986 . . . . . (Apr) 532
Norgard, Milton C., Jan 22, 1987 . . . . . (Apr) 532
Northrup, Judy W., Aug 25, 1986 . . . . . (Feb) 164
Oliedo, George Francis, Sep 21, 1986 . . . . . (Feb) 164
O'Neil, Albert A., Jan 21, 1987 . . . . . (Jun) 796
Palm, Reba Delphine, Aug 24, 1986 . . . . . (Feb) 164
Payne, Robert W., Dec 11, 1986 . . . . . (Apr) 532
Perlstein, Minnie, Dec 17, 1986 . . . . . (Apr) 532
Pilson, Morris J., Feb 8, 1987 . . . . . (Jun) 796
Priest, Ethel H., Nov 7, 1986 . . . . . (Apr) 532
Richards, George M., Feb 21, 1987 . . . . . (Jun) 796
Ritchey, Charles L., Aug 26, 1986 . . . . . (Feb) 164
Robbins, Edward D., Mar 24, 1987 . . . . . (Jun) 796
Robertson, Evalyn, Jan 24, 1987 . . . . . (Jun) 796
Rochex, Francis J., Aug 28, 1986 . . . . . (Feb) 164
Rohlfing, Walter A., Dec 1, 1986 . . . . . (Apr) 532
Rowe, William W., Nov 1986 . . . . . (Apr) 532
Schantz, Guy, Dec 14, 1986 . . . . . (Apr) 532
Schaupp, John B., Sep 13, 1986 . . . . . (Feb) 164
Schmitt, Hugo H., Dec 9, 1986 . . . . . (Apr) 532
Schonberg, Stephen S., Jul 6, 1986 . . . . . (Feb) 164
Schwemley, Robert G., Sep 17, 1986 . . . . . (Apr) 532
Shepard, Richard A., Nov 17, 1986 . . . . . (Apr) 532
Sheppard, William B., Mar 28, 1987 . . . . . (Jun) 796
Sooy, Francis A., Sep 12, 1986 . . . . . (Apr) 532
Thompson, Harvey E., Nov 13, 1986 . . . . . (Apr) 532
Thorpe, H. Harper, Jan 19, 1987 . . . . . (Jun) 796
Tichenor, Ernest I., Oct 6, 1986 . . . . . (Apr) 532
Ticinovich, Dan A., Oct 12, 1986 . . . . . (Apr) 532
Walter, Richard D., Sep 27, 1986 . . . . . (Apr) 532
Westerbeck, Charles W., Oct 29, 1986 . . . . . (Apr) 532
Whitsett, John W., Sep 10, 1986 . . . . . (Apr) 532
Wilson, James R., Sep 30, 1986 . . . . . (Apr) 532
Wilson, Rodney Guy, Mar 7, 1987 . . . . . (Jun) 796
Witt, Everett J., Sep 1, 1986 . . . . . (Apr) 532
Wollack, C. Harold, Jul 19, 1986 . . . . . (Apr) 532
Wong, Donald Loy Hung, Aug 31, 1986 . . . . . (Apr) 532
Wong, Kenneth, Oct 5, 1986 . . . . . (Apr) 532
Young, William Isaac, Nov 3, 1986 . . . . . (Apr) 532

*Montana Medical Association:*
McGregor, Robert J., Jan 1987 . . . . . (Mar) 387

*New Mexico Medical Society:*
Birch, John H., Jan 16, 1987 . . . . . (Jun) 796
Moseley, Robert D., Mar 12, 1987 . . . . . (Jun) 796
Oakes, William R., Feb 1, 1987 . . . . . (Jun) 796
Rice, Lucien G., Jr, Feb 5, 1987 . . . . . (Mar) 387
Tiedemann, John H., Apr 13, 1987 . . . . . (Jun) 796

*Utah State Medical Association:*
Cook, John H., Oct 31, 1986 . . . . . (Mar) 387
Daines, Laura L., Oct 30, 1986 . . . . . (Mar) 387
Ely, Robert S., Mar 5, 1987 . . . . . (Jun) 796
Rich, Charles O., Nov 15, 1986 . . . . . (Mar) 387
Norton, Minthorne D., Mar 19, 1987 . . . . . (Jun) 796
Wintrobe, Maxwell M., Dec 9, 1986 . . . . . (Mar) 387

## SUBJECT INDEX

### A

Abnormal Cellular and Humoral Immunity in Childhood Acute Lymphoblastic Leukemia in Long-term Remission (Clinical Investigation), Jacob Katz, Barbara N. Walter, Geni A. Bennetts, Mitchell S. Cairo . . . . . (Feb) 179
Absence of HIV Antibody Among Dental Professionals Exposed to Infected Patients, Neil M. Flynn, Stephen M. Pollet, James R. Van Horne, Ranveig Elvebakk, Scott D. Harper, James R. Carlson . . . . . (Apr) 439
Access to PaperChase (Correspondence), Howard L. Bleich, Lisa H. Underhill . . . . . (Mar) 366
Achilles Heel of Computer-Initiated Bibliographic Search (Correspondence), Antonios H. Tzamaloukas . . . . . (May) 620
Acquired Immunodeficiency Syndrome, see *AIDS*
Acquired Immunodeficiency Syndrome, see *Gastrointestinal Manifestations of*
Acquired Immunodeficiency Syndrome and Pneumococcal Meningitis, see *32-Year-Old Man With the*
Acquired Immunodeficiency Syndrome Presenting as Schizophrenia, Michael A. Cummings, Kathryn L. Cummings, Mark H. Rapaport, Joseph H. Atkinson, Igor Grant . . . . . (May) 615
Acromegaly Update—Etiology, Diagnosis and Management (Clinical Review), Shlomo Melmed, James A. Fagin . . . . . (Mar) 328
Acute Pancreatitis (Medical Staff Conference), Discussants: James H. Grendell, James Egan . . . . . (May) 598
Acute Promyelocytic Leukemia, Edwin C. Kingsley, Brian G. M. Durie, Harinder S. Garewal . . . . . (Mar) 322
Addendum to Living Will (Correspondence), W. A. Reynolds . . (Apr) 486
Adolescents, see *Screening in Preventive Care for*
[Affirmative Action Programs], see *Distribution of Services to the Underserved*
Against Medical Advice—A Follow-up Study, see *Leaving a Cardiology Service*
Aggressive Concern for Society as a Whole, *In* The Aim of American Medicine Within the Constraints of Today's Society—A Forum,

Murray Klutch . . . . . (Jan) 108
[AIDS], see *Acquired Immunodeficiency Syndrome*
AIDS, see *Dementia and Ataxia in a Patient With*
[AIDS], see
*Gastrointestinal Manifestations of the Acquired Immunodeficiency Syndrome*
AIDS-Related Medical Problems, see *Practical Management of*
AIDS Treatment, see *Lysosomotropic Agents in*
AIDS Vaccine Trial Volunteers Can Be Found (Correspondence), Leon McKusick, Thomas J. Coates, Marcus Conant . . . . . (Feb) 234
AIDS Virus and the Brain (Editorial), Leroy R. Sharer . . . . . (Jan) 88

**Aim of American Medicine Within the Constraints of Today's Society—A Forum:**

What Patients Expect, Carter G. Mosher . . . . . (Jan) 106
A Nuremberg Defense, Glenn S. Vanstrum . . . . . (Jan) 106
Medicine's Problems Reflect Society's, Edward Palmer . . . . . (Jan) 107
Educate, Educate, Educate, R. W. Odell, Jr . . . . . (Jan) 107
Correspondence, Ira E. Bailie . . . . . (Apr) 488
Aggressive Concern for Society as a Whole, Murray Klutch . . . (Jan) 108
Contemporary Aims for American Medicine (Editorial) . . . . . (Jun) 740
Contemporary Aims for American Medicine—1987—A Report on a Forum, Malcolm S. M. Watts . . . . . (Jun) 754

Alcohol and Other Drug Dependence Among Latinos (Correspondence), P. Joseph Frawley . . . . . (May) 620
Alcoholic Patients, see *Using Resistant Behaviors in the Treatment of*
Alcohol Withdrawal Convulsions, see *Clorazepate Use May Prevent*
Aldosterone Associated With Interstitial Nephritis, see *Reversible Renal Resistance to*
Allergy, see *Epitomes*
Allergy, see *Greater Awareness of Sulfite*
Alpha Fetoprotein Screening Program, see *Criticism of the California*

**Alternative Forms of Therapy:**

Using Resistant Behaviors in the Treatment of Alcoholic Patients, La Vera M. Crawley . . . . . (Apr) 499

Ambulatory Monitoring of Uterine Activity (Medical Practice Question) . . . . . (Feb) 240
Amenorrheic Runners, see *Increased Vertebral Bone Mineral in Response to Reduced Exercise in*
American Medicine, see *Contemporary Aims for*
Anemia, see *Clinical Evaluation of*
Anemia, see *Laboratory Evaluation of*
Angiosarcoma of the Liver, see *Atypical Diffuse*
Antimicrobial Agents During Pregnancy, see *Use and Safety of*
[Arizona Health Care Cost Containment System], see *Nonindigents in the AHCCCS Plan*
Artery Embolization, see *Recurrent Hemoptysis Treated by Bronchial*
Artery Surgery, see *Vertebral*
Arthropod Infestations Affecting Humans, see Cheyletiella blakei, *an Ectoparasite of Cats, as Cause of Cryptic*
Ataxia in a Patient with AIDS, see *Dementia and*
Atherosclerosis, see *Dietary Cholesterol and*
Atypical Diffuse Angiosarcoma of the Liver, Gary C. Kanel, Jacob Korula, Choong T. Liew, Robert L. Peters . . . . . (Apr) 482

## B

Bibliographic Search, see *Achilles Heel of Computer—Initiated*
Blood Screening and Evaluation for a Positive Test, see *Fecal Occult*
Blue-Yellow Vision Deficits in Patients With Diabetes (Clinical Investigation), Melissa Rockett, Dorothy Anderle, Alice N. Bessman . . . . . (Apr) 431
Body Odor Caused by Laundry Detergent (Correspondence), Edward C. Sargent . . . . . (Mar) 367
Bone Mineral in Response to Reduced Exercise in Amenorrheic Runners, see *Increased Vertebral*

**Book Reviews:**

Hypertensive Emergencies (Software Review), *Hoffer & Barnett* (Apr) 451
Neurology in Primary Care, *Cantu et al* . . . . . (Feb) 250
Physician-Sponsored HMO Development, *Wagner & Hackenberg* . . . . . (Feb) 250
The Snowbird Diet: 12 Days to a Slender Future—and a Lifetime of Gourmet Eating!, *Robertson & Roberston* . . . . . (Feb) 250
Botulinum Toxin, see *Use of*
Brain, see *AIDS Virus and the*
Bronchial Artery Embolization, see *Recurrent Hemoptysis Treated by*

## C

California Alpha Fetoprotein Screening Program, see *Criticisms of the*
Cancer—Should We Change What We Eat?, see *Diet and*
Cancer Patients, see *Practical Approach to Improving Pain Control in*
Captopril, see *Cough Due to*
Captopril, see *Side-Effect of*
Captopril Therapy, see *Incidence of Cough Associated With*
Cardiac Failure in the Peripartum Period Due to Myopathy of Unknown Cause (Editorial), J. C. Veille . . . . . (Feb) 224
Cardiac Ischmia. Part I—Metabolic and Physiologic Responses (Specialty Conference) . . . . . (Jun) 713
Cardiac Transplantation, see *Peripartum Cardiomyopathy—Successful Treatment With*
Cardiac Transplantation—What Are Acceptable Standards?, see *Survival Following*
Cardiology Service, see *Leaving*
Cardiomyopathy, see *Peripartum*
Carbon Monoxide Poisoning, see *Occult*
Cellular and Humoral Immunity in Childhood Acute Lymphoblastic Leukemia in Long-term Remission, see *Abnormal*
Cerebral Abscesses, see Streptococcus sanguis II *(Viridans) Prosthetic Valve Endocarditis With Myocardial, Splenic and*
Cerebral Emboli in a Young Man, see *Multiple*
Changing Dynamics of Graduate Medical Education—Implications for Decision-Making (Medical Education), Barbara Gerbert, Jonathan A. Showstack, Susan A. Chapman, Steven A. Schroeder . . . . . (Mar) 368
*Cheyletiella blakei*, an Ectoparasite of Cats, as Cause of Cryptic Arthropod Infestations Affecting Humans, Benjamin Keh, Robert S. Lane, Sherry P. Shachter . . . . . (Feb) 192
Child, see *Myasthenia Gravis and Hyperthyrotropinemia in a*
Childhood Acute Lymphoblastic Leukemia in Long-term Remission, see *Abnormal Cellular and Humoral Immunity in*
Children, see *Diagnosis of Obstructive Sleep Apnea in*
Children, see *Epikeratophakia in*
Children, see *Guidelines for the Control of Perinatally Transmitted Human Immunodeficiency Virus Infection and Care of Infected Mothers, Infants and*
Children Who Claim a Prior Penicillin Sensitivity, see *Increased Use of Medical Services and Antibiotics by*
Cholesterol and Atherosclerosis, see *Dietary*
Chronic Mononucleosis in Adults (Information), Paul J. Donald (Feb) 249
Clinical Evaluation and Management of Transient Ischemic Attacks (Medical Progress), John F. Rothrock . . . . . (Apr) 452
Editorial, J. Donald Easton . . . . . (Apr) 474
Clinical Evaluation of Anemia (Editorial), Helen M. Ranney . . (Apr) 473

**Clinical Investigation:**

Increased Vertebral Bone Mineral in Response to Reduced Exercise in Amenorrheic Runners, Jill S. Lindberg, Malcolm R. Powell, Marjorie M. Hunt, Diane E. Ducey, Charles E. Wade . . . . (Jan) 39
Iodine Absorption After Topical Administration, Francine Dela Cruz, Deborah Harper Brown, Jerrold B. Leikin, Cory Franklin, Daniel O. Hryhorczuk . . . . . (Jan) 43
Abnormal Cellular and Humoral Immunity in Childhood Acute Lymphoblastic Leukemia in Long-term Remission, Jacob Katz, Barbara N. Walter, Geni A. Bennetts, Mitchell S. Cairo . . . (Feb) 179
Rapid Fluid Replacement for Severe Hypovolemia—Human Subject Trials, Kenneth V. Iserson, Alan K. Reeter . . . . . (Mar) 313
Blue-Yellow Vision Deficits in Patients With Diabetes, Melissa Rockett, Dorothy Anderle, Alice N. Bessman . . . . (Apr) 431
Serum Potassium Concentration in Hyperglycemia of Diabetes Mellitus With Long-term Dialysis, Antonios H. Tzamaloukas, Pratap S. Avasthi . . . . . (May) 571
Clorazepate Use May Prevent Alcohol Withdrawal Convulsions, Victor G. Haddox, T. George Bidder, Lester E. Waldron, Patricia Derby, Susan M. W. Achen . . . . . (Jun) 695

**Clinical Review:**
Acromegaly Update—Etiology, Diagnosis and Management, Shlomo Melmed, James A. Fagin . . . . . (Mar) 328
Laboratory Evaluation of Anemia, Ralph O. Wallerstein, Jr . . (Apr) 443
Editorial, Helen M. Ranney . . . . . (Apr) 473

Clinician's Guide to Helping Patients Change Behavior (Topics in Primary Care Medicine), Albert R. Martin, Thomas J. Coates (Jun) 751
Clorazepate Use May Prevent Alcohol Withdrawal Convulsions (Clinical Investigation), Victor G. Haddox, T. George Bidder, Lester E. Waldron, Patricia Derby, Susan M. W. Achen . . . (Jun) 695
Cognitive-Procedural Differences (Correspondence), Philip R. Alper . . . . . (Apr) 488

**Commentary:**
Nora's Living Will, E. R. W. Fox . . . . . (Jan) 118
Correspondence, William O. Robertson . . . . . (Apr) 487
Fear of the Unknown, E. R. W. Fox . . . . . (Jun) 759

Computer-Initiated Bibliographic Search, see *Achilles Heel of*
Concept of Cognitive Versus Procedural (Correspondence), Stephen D. Leonard . . . . . (Feb) 235
Philip R. Alper . . . . . (Apr) 488
Consultations in Clinical Ethics—Issues and Questions in 27 Cases (Medical Ethics), John La Puma . . . . . (May) 633
Contemporary Aims for American Medicine (Editorial) . . . . . (Jun) 740
Contemporary Aims for American Medicine—1987—A Report on a Forum, Malcolm S. M. Watts . . . . . (Jun) 754
Convulsions, see *Clorazepate Use May Prevent Alcohol Withdrawal*
Correction: Common AIDS-Related Problems (Correspondence), Nancy Kurahashi . . . . . (Apr) 489
Correction: Computer Programs for Physicians (Correspondence), Lisa H. Underhill, Howard L. Bleich . . . . . (Feb) 236

**Correspondence:**
Access to PaperChase, Howard L. Bleich, Lisa H. Underhill . . (Mar) 366
Achilles Heel of Computer-Initiated Bibliographic Search, Antonios H. Tzamaloukas . . . . . (May) 620
Addendum to Living Will, W. A. Reynolds . . . . . (Apr) 486
AIDS Vaccine Trial Volunteers Can Be Found, Leon McKusick, Thomas J. Coates, Marcus Conant . . . . . (Feb) 234
Alcohol and Other Drug Dependence Among Latinos, P. Joseph Frawley . . . . . (May) 620
Body Odor Caused by Laundry Detergent, Edward C. Sargent . (Mar) 367
Cognitive-Procedural Differences, Philip R. Alper . . . . . (Apr) 488
Concept of Cognitive Versus Procedural, Stephen D. Leonard . . (Feb) 235
Philip R. Alper . . . . . (Apr) 488
Correction: Common AIDS-Related Problems, Nancy Kurahashi (Apr) 489
Correction: Computer Programs for Physicians, Lisa H. Underhill, Howard L. Bleich . . . . . (Feb) 236
Correction: Diagnostic Immunopathy, P. A. Cancilla . . . . . (Jan) 102
Cost-Effectiveness of Fecal Occult Blood Screening, Theodore G. Ganiats, William A. Norcross . . . . . (Apr) 486
Criticisms of the California Alpha Fetoprotein Screening Program, Alan L. Lasnover . . . . . (Jan) 100
David M. Priver . . . . . (Jan) 100
Cultural Change, Social Disintegration and Medicine, Eugene E. Bleck . . . . . (Jun) 749
Definition of Hallucination, R. T. McBratney . . . . . (Mar) 367
Dietary Cholesterol and Atherosclerosis, Ralph S. Wolfstein . . (May) 621
Reply, Susan D. Desmond . . . . . (May) 621
Dollar Mentality, Howard F. Long . . . . . (Jun) 749
Donor Notification for Positive Non-A, Non-B Hepatitis Surrogate Testing, Daniel B. Brubaker, Susie Ukkestad, Byron A. Myhre . . . . . (May) 620
Educating the Public About Life-Style and Nutritional Practices, Ira E. Bailie . . . . . (Apr) 488
Elderly Patients With Dementia, Glen N. Peterson . . . . . (Jan) 101
Alan Paul Zelicoff . . . . . (Jan) 101
Robert A. Fink . . . . . (Jan) 102
Elusiveness of Truth, Laurens P. White . . . . . (Jun) 748
Greater Awareness of Sulfite Allergy Needed, Robert P. Gilbert, Grey Hegman, Claire E. Forsyth . . . . . (Feb) 236
Healing the Healers, John J. Mohr . . . . . (Apr) 489
Heparin Added to Infused Fluids, Basil R. Meyerowitz . . . . . (Jan) 101
Human Immunodeficiency Virus and Hepatitis Testing of Old Bottles of Plasma, B. A. Myhre, S. Yoshida, C. Hilyard Barr . . . . . (Feb) 233
Illness From Organophosphate Exposure, Antonio R. Velasco, Paul G. Barnett, John E. Midtling . . . . . (Apr) 488
Importance of Dive Tables in Scuba Diving, Susan Eile . . . . . (Jun) 750
Incidence of Cough Associated With Captopril Therapy, Gerald R. Dreslinski . . . . . (May) 622
Infection Associated With Joystick Mimicking a Spider Bite, Garwin B. Soe, Larry M. Gersten, Jeanette Wilkins, Michael J. Patzakis, J. Paul Harvey . . . . . (Jun) 748
Lysosomotropic Agents in AIDS Treatment, Bruce L. Kagan . . (Feb) 234
Management of Lumbar Disc Disease, Michael H. Sukoff . . . . (Jun) 748
Matters Gaseous, Frank S. Tolone . . . . . (Jan) 100
Michael A. Sommer . . . . . (Jan) 100
Reply, David F. Altman . . . . . (Jan) 101
Method of Reducing the Iodine Taste of Water Purified in the Wilderness, Byron A. Myhre . . . . . (Mar) 365
Natural Death Acts, William O. Robertson . . . . . (Apr) 487
Nonindigents in the AHCCCS Plan, Donald F. Schaller . . . . . (Jan) 99
Nonsurgical Treatment of Lumbar Disc Sciatica, Gerald G. Hirschberg . . . . . (Mar) 365
Correspondence, Michael H. Sukoff . . . . . (Jun) 748
On Maintaining a Professional Attitude, J. Gary Grant . . . . . (Mar) 365
Physician Production and Influx, Fred A. Baughman, Jr . . . . . (Feb) 236
Role of Irradiation, B. Sharon Cole . . . . . (May) 622
Reply, Francis M. Filloux, Jeannette J. Townsend . . . . . (May) 622
Scuba Diver's Thigh or the Bends?, Robert Fritz . . . . . (Mar) 366
Reply, Arnold H. Greenhouse . . . . . (Mar) 366
Correspondence, Susan Eile . . . . . (Jun) 750
Side-Effect of Captopril and Enalapril, Bennie J. Rossetto . . . . . (Jan) 102
Use of Botulinum Toxin, David M. Hayes . . . . . (Jan) 99
James E. Benecke, Jr . . . . . (Jan) 99
Reply, Nancy M. Newman . . . . . (Jan) 99
Was It Worth It?, Richard M. Cohen . . . . . (Apr) 487
Glenn W. Drumheller . . . . . (Apr) 487
Wright's Law, E. S. Wright . . . . . (Jun) 749

Corticosteroids, see *Fatal* Strongyloides stercoralis *Infection in a Patient Receiving*
Corticotropin-Releasing Factor Test in the Diagnosis of Ectopic ACTH Secretion, Enrico Cagliero, Mara Lorenzi . . . . . (May) 614
Cost-Effectiveness of Fecal Occult Blood Screening (Correspondence), Theodore G. Ganiats, William A. Norcross . . . . . (Apr) 486
Cough Due to Captopril, Edward M. McNally . . . . . (Feb) 226
Correspondence, Gerald R. Dreslinski . . . . . (May) 622
Criticism of the California Alpha Fetoprotein Screening Program (Correspondence), Alan L. Lasnover . . . . . (Jan) 100
David M. Priver . . . . . (Jan) 100
Cross-cultural Sensitivity, see *Teaching Spanish and*
Cryptic Arthropod Infestations Affecting Humans, see Cheyletiella blakei, *an Ectoparasite of Cats, as Cause of*
Cultural Changes, Social Disintegration and Medicine (Correspondence), Eugene E. Bleck . . . . . (Jun) 749
Current Concepts in the Treatment of Tuberculosis (Medical Staff Conference), Discussant: Ira B. Tager . . . . . (Apr) 461

**D**

Death Penalty, see *Physicians and the*
Definition of Hallucination (Correspondence), R. T. McBratney (Mar) 367
Dementia, see *Differentiating Treatable Causes of*
Dementia, see *Elderly Patients With*
Dementia and Ataxia in a Patient With AIDS (Clinicopathologic Conference), Discussants: Gregory L. Clark, Harry V. Vinters (Jan) 68
Dementias, see *Treatable*
Demographic Changes and Health Professions Education (Editorial) . . . . . (Jan) 86
Dental Professionals Exposed to Infected Patients, see *Absence of HIV Antibody Among*
Dental Sealants, see *Preventive Dentistry Update*
Diabetes, see *Blue-Yellow Vision Deficits in Patients With*
Diabetes Mellitus, see *Role of Immunotherapy*
Diabetes Mellitus With Long-term Dialysis, see *Serum Potassium Concentration in Hyperglycemia of*
Diagnosis and Treatment of Smell and Taste Disorders (Editorial), Susan S. Schiffman . . . . . (Apr) 471
Diagnosis of Obstructive Sleep Apnea in Children (Medical Practice Question) . . . . . (Apr) 498
Dialysis, see *Serum Potassium Concentration in Hyperglycemia of*

*Diabetes Mellitus With Long-term*
Diet and Cancer—Should We Change What We Eat? (Medical Staff Conference) . . . (Jan) 73
Dietary Cholesterol and Atherosclerosis (Correspondence), Ralph S. Wolfstein . . . (May) 621
Reply, Susan D. Desmond . . . (May) 621
Differentiating Treatable Causes of Dementia (Editorial), Leon J. Epstein . . . (Jun) 740
Distribution of Services to the Underserved—A Comparison of Minority and Majority Graduates in California (Medical Education), Robert C. Davidson, Roberto Montoya . . . (Jan) 115
Dive Tables in Scuba Diving, see *Importance of*
Dollar Mentality in Health Care Healthy?, see *Is the*
Donor Notification for Positive Non-A, Non-B Hepatitis Surrogate Testing (Correspondence), Daniel B. Brubaker, Susie Ukkestad, Byron A. Myhre . . . (May) 620
Double Vision in a Patient With Lymphoma (Radiologic Case), Todd Kennell, Jonathan M. Levy, Cary J. Stegman . . . (Feb) 241
Drug Dependence Among Latinos, see *Alcohol and Other*

## E

Ectoparasite of Cats, as Cause of Cryptic Arthropod Infestations Affecting Humans, see *Cheyletiella blakei*
Ectopic ACTH Secretion, see *Corticotropin-Releasing Factor Test in the Diagnosis of*

### Editorial Comment:

Stroke in Young People—The Heart of the Matter, Robert G. Hart, Gregory L. Freeman . . . (May) 596

### Editorials:

AIDS Virus and the Brain, Leroy R. Sharer . . . (Jan) 88
Cardiac Failure in the Peripartum Period Due to Myopathy of Unknown Cause, J. C. Veille . . . (Feb) 224
Clinical Evaluation of Anemia, Helen M. Ranney . . . (Apr) 473
Contemporary Aims for American Medicine . . . (Jun) 740
Demographic Changes and Health Professions Education . . . (Jan) 86
Diagnosis and Treatment of Smell and Taste Disorders, Susan S. Schiffman . . . (Apr) 471
Differentiating Treatable Causes of Dementia, Leon J. Epstein . . (Jun) 740
Graduate Medical Education . . . (Mar) 356
Health Care in a Dreamworld . . . (Apr) 471
Correspondence, Eugene E. Bleck . . . (Jun) 749
Immunotherapy—Is the Treatment Worse Than the Disease?, J. Stuart Soeldner . . . (Mar) 356
Intestinal Manifestations of the Acquired Immunodeficiency Syndrome, Donald P. Kotler . . . (Jan) 86
Is the Dollar Mentality in Health Care Healthy? . . . (Mar) 357
Correspondence, Howard F. Long . . . (Jun) 749
Is There an Exercise RDA for Health?, William L. Haskell . . . (Feb) 223
It Can Be a Lethal Instrument . . . (Apr) 475
Primary Care—Does It Have a Future? . . . (May) 613
Surgeon's Approach to Hypoglycemia in Infants and Children, John R. Campbell . . . (May) 612
Transient Ischemic Attacks, J. Donald Easton . . . (Apr) 474
What About 'Private Practice'? . . . (Feb) 223
Whatever Happened to Report MM? . . . (May) 612
$250,000—Was It Worth It? . . . (Jan) 86
Correspondence, Richard M. Cohen . . . (Apr) 487
Glenn W. Drumheller . . . (Apr) 487

Educate, Educate, Educate, *In* The Aim of American Medicine Within the Constraints of Today's Society—A Forum, R. W. Odell, Jr . (Jan) 107
Correspondence, Ira E. Bailie . . . (Apr) 488
Educating the Public About Life-Style and Nutritional Practices (Correspondence), Ira E. Bailie . . . (Apr) 488
Education, see *Changing Dynamics of Graduate Medical*
Education, see *Demographic Changes and Health Professions*
Education, see *Graduate Medical*
Elderly Patients With Dementia (Correspondence), Glen N. Peterson . . . (Jan) 101
Alan Paul Zelicoff . . . (Jan) 101
Robert A. Fink . . . (Jan) 102
Elusiveness of Truth (Correspondence), Laurens P. White . . . (Jun) 748
Emboli in a Young Man, see *Multiple Cerebral*
Emergency Medicine, see *Epitomes*
Enalapril, see *Side-Effect of Captopril and*
Endocarditis, see *Nine Episodes of Infective*
Endocarditis With Myocardial, Splenic and Cerebral Abscesses, see Streptococcus sanguis *II (Viridans) Prosthetic Valve*
Epidemiology of Firearm Deaths Among California Residents (Special Article), Garen J. Wintemute, Stephen P. Teret, Jess F. Kraus (Mar) 374
Epikeratophakia in Children (Medical Practice Question) . . . (Mar) 373

### Epitomes:

**Allergy:**

Mental Effects of Long-term Theophylline Therapy in Children, Clifton T. Furukawa . . . (Jan) 79
The Management of Asthma During Pregnancy, Michael Schatz . (Jan) 80
Nonsedating Antihistamines in the Treatment of Allergic Disease, James P. Kemp, Eli O. Meltzer . . . (Jan) 80
Neuropeptides, Donald G. Payan . . . (Jan) 81
Compliance in Taking Medications, Gerald L. Klein . . . (Jan) 82
Indications for Giving Immune Globulin Intravenously, Joyce J. Schoettler, Douglas C. Heiner . . . (Jan) 82
Leukotrienes, Edward J. Goetzl . . . (Jan) 83
Childhood Asthma and Sinus Disease, Stephen M. Nagy, Jr, Victor E. Cohen . . . (Jan) 83
Late-Phase Reactions and Chronic Asthma, Oscar L. Frick . . . (Jan) 84

**Otolaryngology/Head and Neck Surgery:**

Anosmia—Evaluation and Treatment, Terence M. Davidson . . . (Feb) 219
Microscopically Oriented Histologic Sections for Head and Neck Mucosal Cancer, Terence M. Davidson . . . (Feb) 219
Computed Tomography in Head and Neck Surgery, Michael H. Stevens, H. Ric Harnsberger . . . (Feb) 220
Endoscopic Sinus Operations, Dale H. Rice . . . (Feb) 220
Topical Gentamicin Prophylaxis With Tympanostomy, R. Stan Baker, Richard A. Chole . . . (Feb) 221
Photoactive Therapy for Head and Neck Cancer, Paul J. Donald . (Feb) 221
Anterior Cricoid Split, Craig W. Senders . . . (Feb) 221

**Neurology:**

Neurologic Consequences of Designer Drugs, J. William Langston . . . (Mar) 351
Immunotherapy in Multiple Sclerosis, Jack C. Sipe . . . (Mar) 351
Pseudoseizures, Fumisuke Matsuo . . . (Mar) 352
Should Hypertension in a Patient With Acute Stroke Be Treated?, Arnold H. Greenhouse . . . (Mar) 353
Current Concepts—Alcohol and Brain Damage, Arnold H. Greenhouse . . . (Mar) 354
Neurological Use of Calcium Channel Blocking Agents, John F. Rothrock . . . (Mar) 355

**Orthopedics:**

Shoulder Arthroscopy, Wesley M. Nottage . . . (Apr) 466
Microvascular Transfer of Bone—An Update, Gary K. Frykman (Apr) 466
Immediate Stabilization of Fractures in Patients With Multiple-Systems Injuries, M. W. Chapman . . . (Apr) 467
Recent Advances in the Treatment of Chronic Posttraumatic Osteomyelitis of the Tibia, M. J. Patzakis, J. Wilkins, R. Sherman . . . (Apr) 467
Biopsy of Primary Bone Tumors, Tillman Moore . . . (Apr) 467
Alternatives to Cemented Joint Prostheses, Richard B. Welch . . (Apr) 468
Orthopedic and Soft Tissue Applications of Magnetic Resonance Imaging, David J. Sartoris, Donald Resnick . . . (Apr) 468
Meniscal Repair, Thomas D. Rosenberg, Lonnie E. Paulos, Richard D. Parker . . . (Apr) 469
Sports Footwear, Richard A. Marder . . . (Apr) 469
Osseous and Osteochondral Allografts, Marvin H. Meyers . . . (Apr) 469
Endoprosthetic Limb Salvage Operation for Malignant Bone Tumors, Jeffrey J. Eckardt . . . (Apr) 470

**Emergency Medicine:**

Intraosseous Infusion for Emergency Vascular Access, Judith C. Brillman . . . (May) 603
Sodium Bicarbonate Therapy in Cardiac Arrest, Ricardo Martinez . . . (May) 603
Frostbite, Michael Barmache . . . (May) 604
Ibuprofen Overdose, Brent T. Burton . . . (May) 604
Transcutaneous Cardiac Pacing, Kenneth J. Rhee . . . (May) 605
Evaluating Patients With Tricyclic Antidepressant Overdose for Risk of Complications, Garrett E. Foulke, Michael Callaham . . . (May) 605
Treatment of Snakebite, Robert W. Derlet, Garrett E. Foulke . . (May) 606
Clinical Uses for a New β-Lactamase Inhibitor Antibiotic,

David A. Talan . . . . . (May) 606
Cephalosporins for Bacterial Meningitis, Gary P. Young . . . . . (May) 607
Indications for Hyperbaric Oxygen Therapy, Irving Jacoby . . . (May) 608
Cardiopulmonary Resuscitation and Defibrillation, Mickey Eisenberg . . . . . (May) 608
Expanding the Use of Automatic External Defibrillators to Home and Community, Richard O. Cummins . . . . . (May) 609
Advances in Radiologic Evaluation of Acute Spinal Cord Compression, Robert L. Galli . . . . . (May) 609
Computed Tomography Versus Peritoneal Lavage in Blunt Abdominal Trauma, Michael J. Bresler . . . . . (May) 610
Digoxin-Specific Fab Fragments, George Sternbach . . . . . (May) 610

**General Surgery:**
New Advances in Pancreatic Transplantation, Patrick Soon-Shiong, Geoffrey White . . . . . (Jun) 734
Alternatives to Total Mastectomy for Carcinoma of the Breast, Armando Giuliano . . . . . (Jun) 734
Treatment of Renovascular Hypertension, Fred A. Weaver . . . . (Jun) 735
Anal-Sphincter Saving Operations, Eric W. Fonkalsrud . . . . . (Jun) 736
Treatment of Asymptomatic Gallstones, Richard A. Crass . . . . (Jun) 737
Fine-Needle Aspiration of Thyroid Nodules, Eugene A. Woltering . . . . . (Jun) 737
Heart and Heart-Lung Transplantation, Vaughn A. Starnes, Norman E. Shumway . . . . . (Jun) 738
Brain Death, A. Craig Eddy, Charles L. Rice . . . . . (Jun) 738

---

Esophagoscopy, see *Hospital Admission Following Rigid*
Ethics—Issues and Questions in 27 Cases, see *Consultations in Clinical*
Evaluation and Treatment of Smell Dysfunction, Terence M. Davidson, Alfredo Jalowayski, Claire Murphy, Robert D. Jacobs . . . . . (Apr) 434
Editorial, Susan S. Schiffman . . . . . (Apr) 471
Exercise in Amenorrheic Runners, see *Increased Vertebral Bone Mineral in Response to Reduced*
Exercise RDA for Health, see *Is There*

## F

Factors Associated With Pedestrian-Vehicle Collision Injuries and Fatalities (Public Health), Beth A. Mueller, Frederick P. Rivara, Abraham B. Bergman . . . . . (Feb) 243
Family Physicians in Washington State, Impact on, see *Rising Malpractice Premiums and Obstetrical Practice Patterns*
Fatalities Associated With Off-Road Three-Wheeled All-Terrain Vehicles, see *Injuries and*
Fatal *Strongyloides stercoralis* Infection in a Patient Receiving Corticosteroids, Andrew Yee, C. Thomas Boylen, Thomas Noguchi, Edward C. Klatt, Om P. Sharma . . . . . (Mar) 363
Fear of the Unknown (Commentary), E. R. W. Fox . . . . . (Jun) 759
Fecal Occult Blood Screening and Evaluation for a Positive Test (Topics in Primary Care Medicine), Sarah J. Brendler, Susan W. Tolle . (Jan) 103
Correspondence, Theodore G. Ganiats, William A. Norcross . (Apr) 486
Firearm Deaths, see *Epidemiology of*

## G

Gaseous, see *Matters*
Gastric Balloon for the Treatment of Obesity (Medical Practice Question) . . . . . (Mar) 336
Gastrointestinal Manifestations of the Acquired Immunodeficiency Syndrome (Medical Progress), Vance D. Rodgers, Martin F. Kagnoff . . . . . (Jan) 57
Editorial, Donald P. Kotler . . . . . (Jan) 86
Graduate Medical Education, see *Changing Dynamics of*
Graduate Medical Education (Editorial) . . . . . (Mar) 356
Greater Awareness of Sulfite Allergy Needed (Correspondence), Robert P. Gilbert, Greg Hegman, Claire E. Forsyth . . . . . (Feb) 236

## H

Hallucination, see *Definition of*
Hallucinations, see *Visual*
HBsAg-Positive Asian and Pacific Island Women, see *Program to Provide Hepatitis B Immunoprophylaxis to Infants Born to*
Healing the Healers (Correspondence), John J. Mohr . . . . . (Apr) 489
Health Care, See *Issues in Latino*

**Health Care Delivery:**
Physicians as Patients—The Use of Obstetric Technology in Physician Families, Carin E. Dugowson, Stephen K. Holland . . . . . (Apr) 494
Survival Following Cardiac Transplantation—What Are Acceptable Standards?, Dale G. Renlund, Michael R. Bristow, Nelson A. Burton, Kent W. Jones, S. V. Karwande, William A. Gay, Jr . . . . . (May) 627

---

Health Care in a Dreamworld (Editorial) . . . . . (Apr) 471
Correspondence, Eugene E. Bleck . . . . . (Jun) 749
Health Maintenance, see *Physical Activity and*
Hemoptysis Treated by Bronchial Artery Embolization, see *Recurrent*
Heparin Added to Infused Fluids (Correspondence), Basil R. Meyerowitz . . . . . (Jan) 101
Hepatitis B Immunoprophylaxis to Infants Born to HBsAg-Positive Asian and Pacific Island Women, see *Program to Provide*
Hepatitis Surrogate Testing, see *Donor Notification for Positive Non-A, Non-B*
Hepatitis Testing of Old Bottles of Plasma, see *Human Immunodeficiency Virus*

**History of Medicine:**
Pioneer Transfusionists of Los Angeles, Byron A. Myhre, James H. Cremin . . . . . (Mar) 378

---

HIV Antibody Among Dental Professionals Exposed to Infected Patients, see *Absence of*
Hospital Admission Following Rigid Esophagoscopy (Medical Practice Question) . . . . . (Jan) 42
Human Immunodeficiency Virus and Hepatitis Testing of Old Bottles of Plasma, B. A. Myhre, S. Yoshida, C. Hilyard Barr (Correspondence) . . . . . (Feb) 233
Hyperglycemia of Diabetes Mellitus With Long-term Dialysis, see *Serum Potassium Concentration in*
Hypertension and Hypertensive Crises With Nifedipine, see *Treatment of Severe*
Hyperthyrotropinemia in a Child, see *Myasthenia Gravis and*
Hypoglycemia in Infants and Children, see *Surgeon's Approach to*
Hypoglycemic Syndrome in Infancy and Childhood—A Surgeon's Perspective (Medical Progress), A. R. Moossa, Lori Baker, M. Lavelle-Jones . . . . . (May) 585
Editorial, John R. Campbell . . . . . (May) 612
Hypovolemia, see *Rapid Fluid Replacement*

## I

Idioventricular Rhythm, see *Postdefibrillation*
Illness From Organophosphate Exposure (Correspondence), Antonio R. Velasco, Paul G. Barnett, John E. Midtling . . . . (Apr) 488
Immunodeficiency Virus Infection and Care of Infected Mothers, Infants and Children, see *Guidelines for the Control of Perinatally Transmitted Human*
Immunotherapy—Is the Treatment Worse Than the Disease? (Editorial), J. Stuart Soeldner . . . . . (Mar) 356
Immunotherapy in Type I Diabetes Mellitus, see *Role of*
Importance of Dive Tables in Scuba Diving (Correspondence), Susan Eile . . . . . (Jun) 750
Incidence of Cough Associated With Captopril Therapy (Correspondence), Gerald R. Dreslinski . . . . . (May) 622
Incontinence, see *Urinary*
Increased Use of Medical Services and Antibiotics by Children Who Claim a Prior Penicillin Sensitivity, Michael J. Kraemer, Hope Caprye-Boos, Henry S. Berman . . . . . (Jun) 697
Increased Vertebral Bone Mineral in Response to Reduced Exercise in Amenorrheic Runners (Clinical Investigation), Jill S. Lindberg, Malcolm R. Powell, Marjorie M. Hunt, Diane E. Ducey, Charles E. Wade . . . . . (Jan) 39
Infancy and Childhood, see *Hypoglycemic Syndromes in*
Infants and Children, see *Surgeon's Approach to Hypoglycemia in*
Infants Born to HBsAg-Positive Asian and Pacific Island Women, see *Program to Provide Hepatitis B Immunoprophylaxis to*
Infection Associated With Joystick Mimicking a Spider Bite (Correspondence), Garwin B. Soe, Larry M. Gersten, Jeanette Wilkins, Michael J. Patzakis, J. Paul Harvey . . . . . (Jun) 748
Infective Endocarditis in One Patient, see *Nine Episodes*

**Information:**
Chronic Mononucleosis in Adults, Paul J. Donald . . . . . (Feb) 247
Mitral Valve Prolapse Syndrome—Myth or Reality?, Ronald D. Pollack . . . . . (Mar) 381
Nailing Down the Cause of Perlungual Lesions, Henry Schneiderman, Ann L. Parke . . . . . (Apr) 505
Use and Safety of Antimicrobial Agents During Pregnancy, Anthony W. Chow, Peter J. Jewesson . . . . . (Jun) 761
Leaving a Cardiology Service Against Medical Advice—A Follow-up Study, Herbert N. Ochitill, Randolph C. Byrd, Janet Greene . . (Jun) 765

**Informed Opinion:**
Physicians and the Death Penalty, Kim Marie Thorburn . . . . . (May) 638

Infused Fluids, see *Heparin Added to*
Injuries and Fatalities Associated With Off-Road Three-Wheeled All-Terrain Vehicles (Public Health and Preventive Medicine), C. Mack Sewell, Jeffrey S. Pine, Harry F. Hull . . . . . (Apr) 497
Editorial . . . . . (Apr) 475
Interstitial Nephritis, see *Reversible Renal Resistance to Aldosterone Associated With*
Intestinal Manifestations of the Acquired Immunodeficiency Syndrome (Editorial), Donald P. Kotler . . . . . (Jan) 86

**In the Forefront:**
Teaching Spanish and Cross-cultural Sensitivity to Medical Students, Teresa Gonzalez-Lee, Harold J. Simon . . . . . (Apr) 502

Intravenous Pyelography in Blunt Trauma—A Reappraisal, see *Use of*
Iodine Absorption After Topical Administration (Clinical Investigation), Francine Dela Cruz, Deborah Harper Brown, Jerrold B. Leikin, Cory Franklin, Daniel O. Hryhorczuk . . . . (Jan) 43
Iodine Taste of Water Purified in the Wilderness, see *Method of Reducing*
Irradiation, see *Role of*
Ischemic Attacks, see *Clinical Evaluation and Management of Transient*
Ischemic Attacks, see *Transient*
Is the Dollar Mentality in Health Care Healthy? (Editorial) . . . (Mar) 357
Correspondence, Howard F. Long . . . . . (Jun) 749
Is There an Exercise RDA for Health? (Editorial), William L. Haskell . . . . . (Feb) 223
Issues in Latino Health Care (Medical Staff Conference), Discussant: Eliseo J. Pérez-Stable . . . . . (Feb) 213
It Can Be a Lethal Instrument (Editorial) . . . . . (Apr) 475

**J**

Joystick Mimicking a Spider Bite, see *Infection Associated With*

**L**

Laboratory Evaluation of Anemia (Clinical Review), Ralph O. Wallerstein, Jr . . . . . (Apr) 443
Editorial, Helen M. Ranney . . . . . (Apr) 473
Lactation, see *Stress-Induced Cessation of*
Latino Health Care, see *Issues in*
Latinos, see *Alcohol and Other Drug Dependence Among*
Laundry Detergent, see *Body Odor Caused by*
Leaving a Cardiology Service Against Medical Advice—A Follow-Up Study (Information), Herbert N. Ochitill, Randolph C. Byrd, Janet Greene . . . . . (Jun) 765
Leukemia, see *Acute Promyelocytic*
Leukemia in Long-term Remission, see *Abnormal Cellular and Humoral Immunity in Childhood Acute Lymphoblastic*
Life-Style and Nutritional Practices, see *Educating the Public About*
L'Infarctus du Ventricule Droit—Right Ventricular Infarction in the 1980s (Medical Staff Conference), Discussant: Carlin S. Long (Mar) 344
Liver, see *Atypical Diffuse Angiosarcoma of the*
Living Will, see *Addendum to*
Living Will, see *Nora's*
Lumbar Disc Disease, see *Management of*
Lumbar Disc Sciatica, see *Nonsurgical Treatment of*
Lymphoblastic Leukemia, see *Subacute Leukoencephalopathy Complicating Acute*
Lymphoma, see *Double Vision in a Patient With*
Lysosomotropic Agents in AIDS Treatment (Correspondence), Bruce L. Kagan . . . . . (Feb) 234

**M**

Malpractice Premiums and Obstetrical Practice Patterns—The Impact on Family Physicians in Washington State, see *Rising*
Management of Lumbar Disc Disease (Correspondence), Michael H. Sukoff . . . . . (Jun) 748
Matters Gaseous (Correspondence), Frank S. Tolone . . . . . (Jan) 100
Michael A. Sommer . . . . . (Jan) 100
Reply, David F. Altman . . . . . (Jan) 101
Medical Advice—A Follow-Up Study, see *Leaving a Cardiology Service Against*

**Medical Education:**
Distribution of Services to the Underserved—A Comparison of Minority and Majority Graduates in California, Robert C. Davidson, Roberto Montoya . . . . . (Jan) 115
Editorial . . . . . (Jan) 86
The Changing Dynamics of Graduate Medical Education—Implications for Decision-Making, Barbara Gerbert, Jonathan A. Showstack, Susan A. Chapman, Steven A. Schroeder . . . . . (Mar) 368
Editorial . . . . . (Mar) 356

**Medical Ethics:**
Consultations in Clinical Ethics—Issues and Questions in 27 Cases, John La Puma . . . . . (May) 633

**Medical Practice Questions:**
Ambulatory Monitoring of Uterine Activity . . . . . (Feb) 240
Diagnosis of Obstructive Sleep Apnea in Children . . . . . (Apr) 498
Epikeratophakia in Children . . . . . (Mar) 373
Gastric Balloon for the Treatment of Obesity . . . . . (Mar) 336
Hospital Admission Following Rigid Esophagoscopy . . . . . (Jan) 42
Vertebral Artery Surgery . . . . . (Feb) 187

**Medical Progress:**
Gastrointestinal Manifestations of the Acquired Immunodeficiency Syndrome, Vance D. Rodgers, Martin F. Kagnoff . . . . . (Jan) 57
Editorial, Donald P. Kotler . . . . . (Jan) 86
Physical Activity and Health Maintenance—Exactly What Is Known?, James R. Phelps . . . . . (Feb) 200
Editorial, William L. Haskell . . . . . (Feb) 223
The Role of Immunotherapy in Type I Diabetes Mellitus, Mitchell E. Geffner, Barbara M. Lippe . . . . . (Mar) 337
Editorial, J Stuart Soeldner . . . . . (Mar) 356
Clinical Evaluation and Management of Transient Ischemic Attacks, John F. Rothrock . . . . . (Apr) 452
Editorial, J. Donald Easton . . . . . (Apr) 474
Hypoglycemic Syndrome in Infancy and Childhood—A Surgeon's Perspective, A. R. Moosa, Lori Baker, M. Lavelle-Jones . . . (May) 585
Editorial, John R. Campbell . . . . . (May) 612
Treatable Dementias, Michael E. Mahler, Jeffrey L. Cummings, D. Frank Benson . . . . . (Jun) 705
Editorial, Leon J. Epstein . . . . . (Jun) 740

**Medical Staff Conferences:**
Diet and Cancer—Should We Change What We Eat?, Discussant: Susan Desmond . . . . . (Jan) 73
Correspondence, Ralph S. Wolfstein . . . . . (May) 621
Reply, Susan Desmond . . . . . (May) 621
Issues in Latino Health Care, Discussant: Eliseo J. Pérez-Stable . (Feb) 213
Correspondence, P. Joseph Frawley . . . . . (May) 620
L'Infarctus du Ventricule Droit—Right Ventricular Infarction in the 1980s, Discussant: Carlin S. Long . . . . . (Mar) 344
Current Concepts in the Treatment of Tuberculosis, Discussant: Ira B. Tager . . . . . (Apr) 461
Acute Pancreatitis, Discussants: James H. Grendell, James Egan (May) 598
Peptic Ulcer Disease—Pathophysiology and Current Medical Management, Discussant: Bruce F. Scharschmidt . . . . . (Jun) 724

Medicine, see *Cultural Changes, Social Disintegration and*

Medicine's Problems Reflect Societys, *In* The Aim of American Medicine Within the Constraints of Today's Society—A Forum, Edward Palmer . . . . . (Jan) 107
Method of Reducing the Iodine Taste of Water Purified in the Wilderness (Correspondence), Byron A. Myhre . . . . . (Mar) 365
Minority and Majority Graduates, Comparison of, see *Distribution of Services to the Underserved*
Mitral Valve Prolapse Syndrome—Myth or Reality? (Information), Ronald D. Pollack . . . . . (Mar) 381
Monitoring of Uterine Activity, see *Ambulatory*
Mononucleosis in Adults, see *Chronic*
Multiple Cerebral Emboli in a Young Man (Clinicopathologic Conference), Mark P. Nespeca, Jeannette J. Townsend . . . . (May) 589
Editorial Comment, Robert G. Hart, Gregory L. Freeman . . (May) 596
Myasthenia Gravis and Hyperthyrotropinemia in a Child, Susan M. Scott, Alan H. Klein, Jo Anne Brasel . . . . . (Apr) 476
Myocardial, Splenic and Cerebral Abscesses, see Streptococcus sanguis II *(Viridans) Prosthetic Valve Endocarditis With*
Myocardial Ischemia, see *Treatment of*

## N

Nailing Down the Cause of Periungual Lesions (Information), Henry Schneiderman, Ann L. Parke . . . . . (Apr) 505
Natural Death Acts (Correspondence), William O. Robertson . . (Apr) 487
Nephritis, see *Reversible Renal Resistance to Aldosterone Associated With Interstitial*
Neurology, see *Epitomes*
Nifedipine, see *Treatment of Severe Hypertension and Hypertensive Crises With*
Nine Episodes of Infective Endocarditis in One Patient—A New Record, Jay Simonson, Virginia Mylo Schaaf, John Mills . . . (Jan) 96
Editorial . . . . . (Jan) 86
Nonindigents in the AHCCS Plan (Correspondence), Donald F. Schaller . . . . . (Jan) 99
Nonsurgical Treatment of Lumbar Disc Sciatica (Correspondence), Gerald G. Hirschberg . . . . . (Mar) 365
Correspondence, Michael H. Sukoff . . . . . (Jun) 748
Nora's Living Will (Commentary), E. R. W. Fox . . . . . (Jan) 118
Correspondence, William O. Robertson . . . . . (Apr) 487
Nuremberg Defense, *In* The Aim of American Medicine Within the Constraints of Today's Society—A Forum, Glenn S. Vanstrum . (Jan) 106
Nutritional Practices, see *Educating the Public About Life-Style and*

## O

Obesity, see *Gastric Balloon for the Treatment of*
Obstetrical Practice Patterns, see *Rising Malpractice Premiums and*
Obstetric Technology in Physician Families, see *Physicians as Patients—The Use of*
Obstructive Sleep Apnea in Children, see *Diagnosis of*
Occult Carbon Monoxide Poisoning, John N. Kirkpatrick . . . . . (Jan) 52
Off-Road Three-Wheeled All-Terrain Vehicles, see *Injuries and Fatalities Associated With*
On Maintaining a Professional Attitude (Correspondence), J. Gary Grant . . . . . (Mar) 365
Organophosphate Exposure, see *Illness From*
Otolaryngology/Head and Neck Surgery, see *Epitomes*

## P

Pain Control in Cancer Patients, see *Practical Approach to Improving*
Pancreatitis, see *Acute*
PaperChase, see *Access to*
Patients With Dementia, see *Elderly*
Penicillin Sensitivity, see *Increased Use of Medical Services and Antibiotics by Children Who Claim a Prior*
Peptic Ulcer Disease—Pathophysiology and Current Medical Management (Medical Staff Conference), Discussant: Bruce F. Scharschmidt . . . . . (Jun) 724
Peripartum Cardiomyopathy—Successful Treatment With Cardiac Transplantation, Samuel G. Joseph . . . . . (Feb) 230
Editorial, J. C. Veille . . . . . (Feb) 224
Periungual Lesions, see *Nailing Down the Cause*
Pheochromocytoma, see *Sarcoidosis*
Physical Activity and Health Maintenance—Exactly What Is Known? (Medical Progress), James R. Phelps . . . . . (Feb) 200
Editorial, William L. Haskell . . . . . (Feb) 223
Physician Production and Influx (Correspondence), Fred A. Baughman, Jr . . . . . (Feb) 236
Physicians and the Death Penalty (Informed Opinion), Kim Marie Thorburn . . . . . (May) 638
Physicians as Patients—The Use of Obstetric Technology in Physician Families (Health Care Delivery), Carin E. Dugowson, Stephen K. Holland . . . . . (Apr) 494
Pioneer Transfusionists of Los Angeles (History of Medicine), Byron A. Myhre, James H. Cremin . . . . . (Mar) 378
Plasma, see *Human Immunodeficiency Virus and Hepatitis Testing of Old Bottles of*
Pneumococcal Meningitis, see *32-Year-Old Man With the Acquired Immunodeficiency Syndrome and*
Poisoning, see *Occult Carbon Monoxide*
Postdefibrillation Idioventricular Rhythm—A Salvageable Condition, Jerome R. Hoffman, Lynne Warner Stevenson . . . . . (Feb) 188
Potassium Concentration in Hyperglycemia of Diabetes Mellitus with Long-term Dialysis, see *Serum*
Practical Approach to Improving Pain Control in Cancer Patients, Malcolm L. Brigden, Jeffrey B. Barnett . . . . . (May) 580
Practical Management of Common AIDS-Related Medical Problems (Topics in Primary Care Medicine), Harry Hollander . . . . . (Feb) 237
Correspondence, Nancy Kurahashi . . . . . (Apr) 489
Practitioner's Guide to Treatment Selection in Psychiatry (Seminars in Health Care Delivery), Allen Frances, John Clarkin, Samuel Perry . . . . . (Jan) 109
Pregnancy, see *Use and Safety of Antimicrobial Agents*
Preserving Renal Function in Surgical Patients, Connie Whiteside-Yim, Faith T. Fitzgerald . . . . . (Mar) 316
Preventive Care for Adolescents, see *Screening in*
Preventive Dentistry Update—Dental Sealants (Public Health and Preventive Medicine), Robert Isman, Kenneth W. Kizer . . . . (May) 631
Primary Care—Does It Have a Future? (Editorial) . . . . . (May) 613
'Private Practice,' see *What About*
Professional Attitude, see *On Maintaining*
Program to Provide Hepatitis B Immunoprophylaxis to Infants Born to HBsAg-Positive Asian and Pacific Island Women, Karl C. Klontz . . . . . (Feb) 195
Promyelocytic Leukemia, see *Acute*
Prosthetic Valve Endocarditis With Myocardial, Splenic and Cerebral Abscesses, see Streptococcus sanguis II *(Viridans)*
Psittacosis, Stephen J. McPhee, Blair Erb, William Harrington (Jan) 91
Psychiatry, see *Practitioner's Guide to Treatment Selection in*

**Public Health:**

Factors Associated With Pedestrian-Vehicle Collision Injuries and Fatalities, Beth A. Mueller, Frederick P. Rivara, Abraham B. Bergman . . . . . (Feb) 243

**Public Health and Preventive Medicine:**

Injuries and Fatalities Associated With Off-Road Three-Wheeled All-Terrain Vehicles, C. Mack Sewell, Jeffrey S. Pine, Harry F. Hull . . . . . (Apr) 497
Editorial . . . . . (Apr) 475
Preventive Dentistry Update—Dental Sealants, Robert Isman, Kenneth W. Kizer . . . . . (May) 631
Pyelography in Blunt Trauma—A Reappraisal, see *Use of Intravenous*

## R

**Radiologic Case:**

Double Vision in a Patient With Lymphoma, Todd Kennell, Jonathan M. Levy, Cary J. Stegman . . . . . (Feb) 241
Rapid Fluid Replacement for Severe Hypovolemia—Human Subject Trials (Clinical Investigation), Kenneth V. Iserson, Alan K. Reeter . . . . . (Mar) 313
Recurrent Hemoptysis Treated by Bronchial Artery Embolization,

Mark G. Stein, Michael S. Stulbarg, W. Richard Webb, Gorden Gamsu . . . . . (Mar) 358
Refractory Scleritis Due to Wegener's Granulomatosis, Ernest J. Hodges, Stephen Turner, Robert B. Doud . . . . . (Mar) 361
Renal Function in Surgical Patients, see *Preserving*
Report MM, see *Whatever Happened to*
Resistant Behaviors in the Treatment of Alcoholic Patients, see *Using*
Reversible Renal Resistance to Aldosterone Associated With Interstitial Nephritis, John J. Regan, Jr, Charles S. Greenberg, Arshag D. Mooradian, Nancy Staley, Frank Q. Nuttall . . . . . (Jun) 742
Right Ventricular Infarction in the 1980s, see *L'Infarctus du Ventricular Droit*
Rigid Esophagoscopy, see *Hospital Admission Following*
Rising Malpractice Premiums and Obstetric Practice Patterns—The Impact on Family Physicians in Washington State (Special Article), Roger A. Rosenblatt, Craig L. Wright . . . . . (Feb) 246
Role of Immunotherapy in Type I Diabetes Mellitus (Medical Progress), Mitchell E. Geffner, Barbara M. Lippe . . . . . (Mar) 337
Editorial, J. Stuart Soeldner . . . . . (Mar) 356
Role of Irradiation (Correspondence), B. Sharon Cole . . . . . (May) 622
Reply, Francis M. Filloux, Jeannette J. Townsend . . . . . (May) 622
Runners, see *Increased Vertebral Bone Mineral in Response to Reduced Exercise in Amenorrheic*

## S

Sarcoidosis and Pheochromocytoma, Kevin M. Murray, Richard F. Schillaci . . . . . (Jun) 745
Sarcoidosis Presenting as Chronic Thrombocytopenia, Stephen K. Field, Man-Chiu Poon . . . . . (Apr) 481
Schizophrenia, see *Acquired Immunodeficiency Syndrome Presenting as*
Sciatica, see *Nonsurgical Treatment of Lumbar Disc*
Scleritis Due to Wegener's Granulomatosis, see *Refractory*
Screening in Preventive Care for Adolescents (Topics in Primary Care Medicine), Paula Braveman, Kathleen E. Toomey . . . . . (Apr) 490
Screening Program, see *Criticism of the California Alpha Fetoprotein*
Scuba Diver's Thigh or the Bends? (Correspondence), Robert Fritz . . . . . (Mar) 366
Reply, Arnold H. Greenhouse . . . . . (Mar) 366
Correspondence, Susan Eile . . . . . (Jun) 750
Scuba Diving, see *Importance of Dive Tables in*

### Seminars in Health Care Delivery:

Practitioner's Guide to Treatment Selection in Psychiatry, Allen Frances, John Clarkin, Samuel Perry . . . . . (Jan) 109

---

Serum Potassium Concentration in Hyperglycemia of Diabetes Mellitus With Long-term Dialysis (Clinical Investigation), Antonios H. Tzamaloukas, Pratap S. Avasthi . . . . . (May) 571
Side Effect of Captopril and Enalapril (Correspondence), Bennie J. Rossetto . . . . . (Jan) 102
Sleep Apnea in Children, see *Diagnosis of Obstructive*
Smell and Taste Disorders, see *Diagnosis and Treatment of*
Smell Dysfunction, see *Evaluation and Treatment of*
Social Disintegration and Medicine, see *Cultural Changes*
Spanish and Cross-cultural Sensitivity, see *Teaching*

### Special Articles:

Rising Malpractice Premiums and Obstetric Practice Patterns—The Impact on Family Physicians in Washington State, Roger A. Rosenblatt, Craig L. Wright . . . . . (Feb) 246
The Epidemiology of Firearm Deaths Among Residents of California, Garen J. Wintemute, Stephen P. Teret, Jess F. Kraus . . . . . (Mar) 374

---

### Specialty Conferences:

Dementia and Ataxia in a Patient With AIDS (Clinicopathologic Conference From Center for the Health Sciences, UCLA School of Medicine, Los Angeles), Discussants: Gregory L. Clark, Harry V. Vinters . . . . . (Jan) 68
Editorial, Leroy R. Sharer . . . . . (Jan) 88
Subacute Leukoencephalopathy Complicating Acute Lymphoblastic Leukemia (Clinicopathologic Conference from University of Utah School of Medicine), Discussants: Francis M. Filloux, Jeannette J. Townsend . . . . . (Feb) 207
Correspondence, B. Sharon Cole . . . . . (May) 622
Reply, Francis M. Filloux, Jeannette J. Townsend . . . . . (May) 622
Multiple Cerebral Emboli in a Young Man, Mark P. Nespeca, Jeannette J. Townsend . . . . . (May) 589
Editorial Comment, Robert G. Hart, Gregory L. Freeman . . (May) 596
Cardiac Ischemia. Part I—Metabolic and Physiologic Responses (UCLA Interdepartmental Conference), Moderator: Glenn A. Langer; Discussants: James N. Weiss, Heinrich R. Schelbert . . . . . (Jun) 713

---

Spider Bite, see *Infection Associated With Joystick Mimicking*
Streptococcus sanguis II (Viridans) Prosthetic Valve Endocarditis With Myocardial, Splenic and Cerebral Abscesses, Steven G. Young, Thomas Davee, Joshua Fierer, Mitch K. Morey. . . . . (Apr) 479
Stress-Induced Cessation of Lactation, R. H. A. Ruvalcaba . . . (Feb) 228
Stroke in Young People—The Heart of the Matter (Editorial Comment), Robert G. Hart, Gregory L. Freeman . . . . . (May) 596
*Strongyloides stercoralis* Infection in a Patient Receiving Corticosteroids, see *Fatal*
Subacute Leukoencephalopathy Complicating Acute Lymphoblastic Leukemia (Clinicopathologic Conference From University of Utah School of Medicine), Discussants: Francis M. Filloux, Jeannette J. Townsend . . . . . (Feb) 207
Sulfite Allergy, see *Greater Awareness of*
Surgeon's Approach to Hypoglycemia in Infants and Children (Editorial), John R. Campbell . . . . . (May) 612
Surgeon's Perspective, see *Hypoglycemic Syndromes in Infancy and Childhood—A*
Surgery, see *Vertebral Artery*
Surgical Patients, see *Preserving Renal Function in*
Survival Following Cardiac Transplantation—What Are Acceptable Standards? (Health Care Delivery), Dale G. Renlund, Michael R. Bristow, Nelson A. Burton, Kent W. Jones, S. V. Karwande, William A. Gay, Jr . . . . . (May) 627

## T

Taste Disorders, see *Diagnosis and Treatment of Smell and*
Teaching Spanish and Cross-cultural Sensitivity to Medical Students (In the Forefront), Teresa Gonzalez-Lee, Harold J. Simon . . . . . (Apr) 502
32-Year-Old Man With the Acquired Immunodeficiency Syndrome and Pneumococcal Meningitis, Diane V. Havlir, Mallory D. Witt, Merle Sande . . . . . (May) 618
Three-Wheeled All-Terrain Vehicles, see *Injuries and Fatalities Associated With Off-Road*
Thrombocytopenia, see *Sarcoidosis Presenting as Chronic*

### Topics in Primary Care Medicine:

Fecal Occult Blood Screening and Evaluation for a Positive Test, Sarah J. Brendler, Susan W. Tolle . . . . . (Jan) 103
Correspondence, Theodore G. Ganiats, William A. Norcross . (Apr) 486
Practical Management of Common AIDS-Related Medical Problems, Harry Hollander . . . . . (Feb) 237
Correspondence, Nancy Kurahashi . . . . . (Apr) 489
Screening in Preventive Care for Adolescents, Paula Braveman, Kathleen E. Toomey . . . . . (Apr) 490
Urinary Incontinence, Kurt Kroenke, Douglas Corrie . . . . . (May) 623
Clinician's Guide to Helping Patients Change Behavior, Albert R. Martin, Thomas J. Coates . . . . . (Jun) 751

---

Toxin, see *Use of Botulinum*
Transfusionists of Los Angeles, see *Pioneer*
Transient Ischemic Attacks, see *Clinical Evaluation and Management of*
Transient Ischemic Attacks (Editorial), J. Donald Easton . . . . . (Apr) 474
Transplantation—What Are Acceptable Standards?, see *Survival Following Cardiac*
Trauma, see *Use of Intravenous Pyelography in Blunt*
Treatable Dementias (Medical Progress), Michael E. Mahler, Jeffrey L. Cummings, D. Frank Benson . . . . . (Jun) 705
Editorial, Leon J. Epstein . . . . . (Jun) 740
Treatment of Severe Hypertension and Hypertensive Crises With Nifedipine, Mark C. Houston . . . . . (Jun) 701
Tuberculosis, see *Current Concepts in the Treatment of*
$250,000—Was It Worth It? (Editorial) . . . . . (Jan) 86

U

Ulcer Disease—Pathophysiology and Current Medical Management, see *Peptic*
Underserved [Populations], see *Distribution of Services to the*
Unknown, see *Fear of the*
Urinary Incontinence (Topics in Primary Care Medicine), Kurt Kroenke, Douglas Corrie . . . . . (May) 623
Use and Safety of Antimicrobial Agents During Pregnancy (Information), Anthony W. Chow, Peter J. Jewesson . . . . . (Jun) 761
Use of Botulinum Toxin (Correspondence), David M. Hayes . . . (Jan) 99
James E. Benecke, Jr . . . . . (Jan) 99
Reply, Nancy M. Newman . . . . . (Jan) 99
Use of Intravenous Pyelography in Blunt Trauma—A Reappraisal, Jerome R. Hoffman, Robert R. Simon, Marc Smith, Glenn Strom, Larry J. Baraff . . . . . (May) 576
Using Resistant Behaviors in the Treatment of Alcoholic Patients (Alternative Forms of Therapy), La Vera M. Crawley . . . . . (Apr) 499
Uterine Activity, see *Ambulatory Monitoring of*

V

Vaccine Trial Volunteers Can Be Found, see *AIDS*
Vertebral Artery Surgery (Medical Practice Question) . . . . . (Feb) 187
Vertebral Bone Mineral in Response to Reduced Exercise in Amenorrheic Runners, see *Increased*
Vertigo, see *Wegener's Granulomatosis Presenting as*
Vision Deficits in Patients With Diabetes, see *Blue-Yellow*
Vision in a Patient With Lymphoma, see *Double*
Visual Hallucinations—Clinical Occurrence and Use in Differential Diagnosis, Jeffrey L. Cummings, Bruce L. Miller . . . . . (Jan) 46
Correspondence, R. T. McBratney . . . . . (Mar) 367

W

[Washington State], see *Factors Associated With Pedestrian-Vehicle Collision Injuries and Fatalities*
Washington State, see *Rising Malpractice Premiums and Obstetric Practice Patterns—The Impact on Family Physicians in*
Was It Worth It? (Correspondence), Richard M. Cohen . . . . . (Apr) 487
Glenn W. Drumheller . . . . . (Apr) 487
Water Purified in the Wilderness, see *Method of Reducing the Iodine Taste*
Wegener's Granulomatosis, see *Refractory Scleritis Due to*
Wegener's Granulomatosis Presenting as Vertigo, Richard W. Bennett, Larry V. Staker . . . . . (Mar) 359
What About 'Private Practice'? (Editorial) . . . . . (Feb) 223
Whatever Happened to Report MM? (Editorial) . . . . . (May) 612
What Patients Expect, *In* The Aim of American Medicine Within the Constraints of Today's Society—A Forum, Carter G. Mosher . (Jan) 106
Wilderness, see *Method of Reducing the Iodine Taste of Water Purified in the*
Will, see *Nora's Living*
Will, see *Addendum to Living*
Withdrawal Convulsions, see *Clorazepate Use May Prevent Alcohol*
Wright's Law (Correspondence), Edwin S. Wright . . . . . (Jun) 749

Y

Young People, see *Stroke in*

# MPM-1000

## MEDICAL PRACTICE MANAGEMENT SYSTEM

THE COMPLETE PRESCRIPTION FOR OFFICE PRODUCTIVITY FROM CURTIS 1000 INFORMATION SYSTEMS

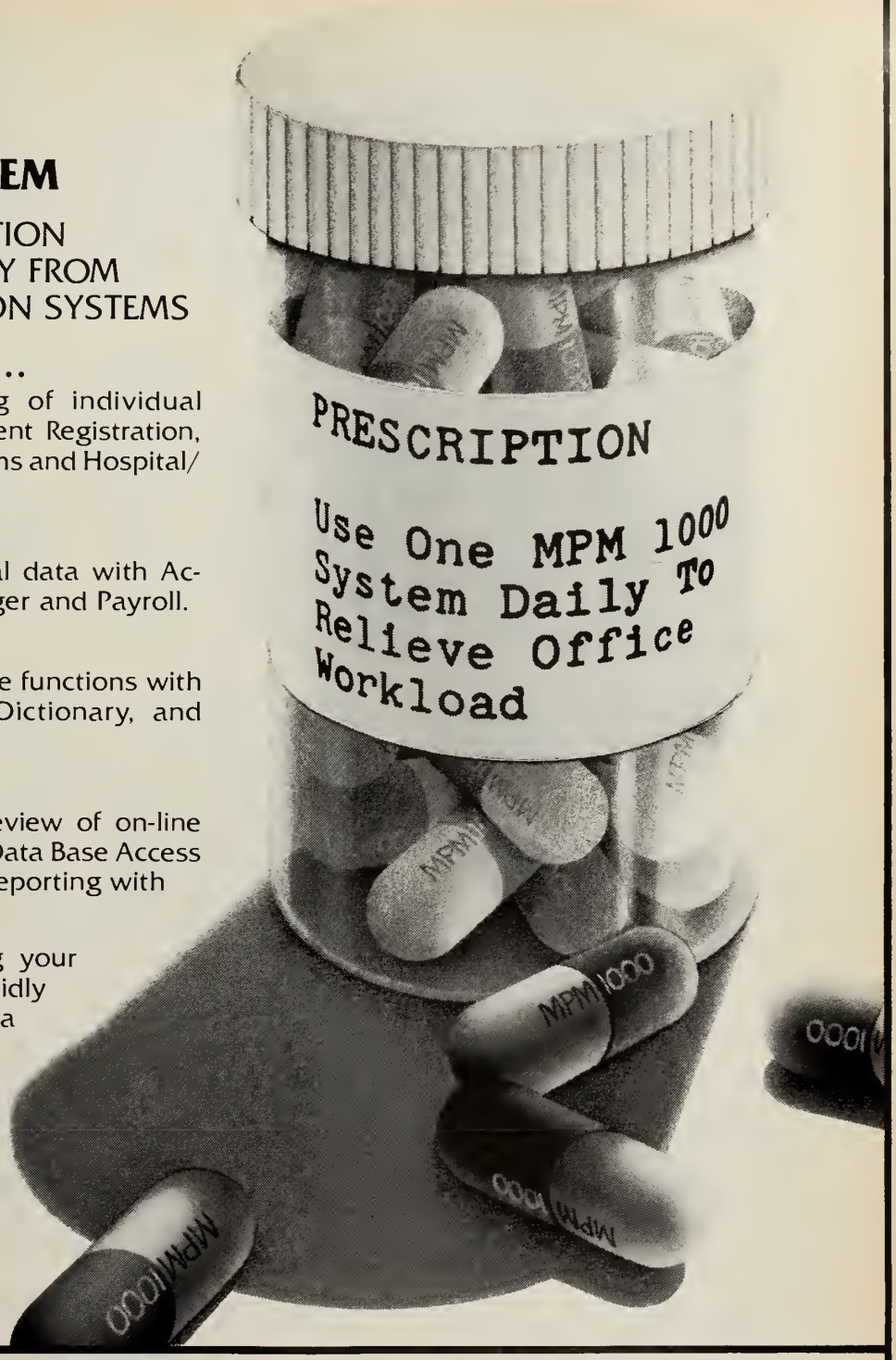
**$R_x$ for Improved Patient Care...**
MPM-1000 speeds handling of individual patient information with Patient Registration, Patient Billing, Electronic Claims and Hospital/ Physician Network.

**$R_x$ for Profitability...**
MPM-1000 organizes financial data with Accounts Payable, General Ledger and Payroll.

**$R_x$ for Efficiency...**
MPM-1000 controls daily office functions with Word Processing, Medical Dictionary, and Inventory Control.

**$R_x$ for Productivity...**
MPM-1000 allows in-office review of on-line clinical data through Remote Data Base Access and extensive management reporting with Query Report Generator.

Whether you're just starting your medical office or belong to a rapidly growing practice, MPM-1000 is a complete Medical Practice Management System designed to meet your needs now and in the future.




**For more information call or write:**
**Curtis 1000 Information Systems**
Western Regional Office
7011 Cort Rosa, P.O. Box 141
Pleasanton, CA 94566
**(415) 484-2036** or **1-800-241-4780**

Curtis 1000 INFORMATION SYSTEMS

Western Regional Office
7011 Cort Rosa
P.O. Box 141
Pleasanton, CA 94566

Please tell me more about your Prescription for Productivity

Name: _____

Practice Name: _____

Address: _____

City: _____ State _____ Zip _____

Phone: _____ Specialty: _____

Number of Physicians: _____

MPM 1000
MEDICAL PRACTICE MANAGEMENT SYSTEM

# Classified Advertisements

The rate for each insertion is **$6 per line** (average six words per line) **with five line ($30) minimum.** Box number charge: $5 each month.

**Classified display rates $50 per inch.**

Copy for classified advertisements should be received not later than **25th of the second month preceding issue. All copy must be typed or printed.** • Classified advertisers using Box Numbers forbid the disclosure of their identity; your inquiries in writing will be forwarded to Box Number advertisers. The right is reserved to reject or modify all classified advertising copy in conformity with the decisions of the Advertising Committee.

**Please Type or Print Advertising Copy**

## Classified Advertisements Are Payable in Advance

CLASSIFIED ADVERTISEMENTS
THE WESTERN JOURNAL OF MEDICINE
P.O. BOX 7602, SAN FRANCISCO, CA 94120-7602

### PHYSICIANS WANTED

**ORTHOPEDIC SURGEON.** F/T Orthopedic Surgeon to join growing multispecialty group in southern California. Salary plus malpractice and benefits. Great potential for right physician; individual ownership. Send CV to Number 18, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

**OREGON.** General Internist sought for busy practice. Multispecialty group of 10 physicians, 38 miles from Portland. CV to Administrator, Physicians' Medical Center, PC, 420 E. Fifth St, McMinnville, OR 97128; (503) 472-6161.

**NEAR STANFORD.** Six Internists, all sub-specialty trained and members of clinical faculty at Stanford, interested in an Associate with subspecialty interest and training. Should be well grounded in Internal Medicine. Send CV to Dr Bigler, El Camino Internal Medical Group, 125 South Dr, Mountain View, CA 94040.

**ADDITIONAL INTERNIST NEEDED** for busy 5-physician multispecialty group. Beautiful, well-equipped six-year-old office just 75 feet from 34-bed hospital with ICU/CCU unit. This all Board certified group houses three Family Practitioners, two General Surgeons, and one Internist. Coastal retirement town offers top-notch school system and excellent array of activities. Located just 75 easy miles from Portland adds even more cultural and shopping opportunities. For further information contact Rick Bigger days at North Coast Medical Center, PC, Seaside, Oregon; (503) 738-9551.

**NORTHERN CALIFORNIA.** FP/IM physicians needed to staff ambulatory care clinics in the Central Valley region of California. Paid malpractice and excellent benefit package. Incentive plus guarantee. If interested, please contact SEMG, PO Box 214584, Sacramento, CA 95821.

**PEDIATRICIAN BC/BE** for hospital-based teaching practice. Interest and training in neonatology and critical care pediatrics preferred. Join two full-time pediatricians and two full-time neonatologists in hospital with Level II ICN and busy inpatient and out-patient services. Paid malpractice. Salary negotiable based on training and experience. Submit CV and references to Patricia A. Dixon, MD, Director, Pediatrics/Neonatal Services, San Joaquin General Hospital, PO Box 1020, Stockton, CA 95201; (209) 468-6600. AA/EOE.

### PHYSICIANS WANTED

**HEMATOLOGIST-ONCOLOGIST** to join established multiethnic urban northern California private practice by August 1987. Second language of Mandarin, Cantonese, or Spanish necessary. Send CV and references. Please reply to Number 26, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

**PRACTICE FAMILY MEDICINE** with the people in rural Iowa communities where the quality of life is superb. Solo and group practice opportunities available including guaranteed salaries and full benefit packages. For an immediate response please call 1 (800) 247-3121, ext 8204 (USA).

**INPATIENT TRAINING DIRECTOR—GENERAL INTERNIST OR FAMILY PHYSICIAN.** The UCLA/Santa Monica Hospital Medical Center Family Practice Residency Program is seeking a Board certified General Internist or Family Physician with special interest in clinical teaching of residents. Major responsibilities include extensive inpatient teaching and direction of an internal medicine service. The position also emphasizes patient care and curriculum administration. Research skills are desirable. Please send CV to Charles Payton, MD, Family Practice Residency Program, 1225 Fifteenth St, Santa Monica, CA 90404.

**NEPHROLOGIST/INTERNIST.** Opening available in 160 plus physician group. Need additional Nephrologist/Internist in a busy and fulfilling HMO practice in the San Francisco bay area. Excellent working conditions. Ample opportunities for house staff teaching, clinical faculty appointment, cooperative group participation. Competitive salary. Superb benefit package. Reply with CV to William Peters, MD, Department of Internal Medicine, The Permanente Medical Group, 260 International Cir, San Jose, CA 95119. An Equal Opportunity/Affirmative Action Employer.

**NEW MEXICO—TAOS AND LAS VEGAS.** Excellent full-time hospital emergency department positions are currently available with Spectrum in Taos and Las Vegas. Moderate to low volume emergency departments. Excellent medical and nursing support. Guaranteed rate of reimbursement, occurrence malpractice insurance coverage, CME allowance, reimbursement of professional dues. For additional information on these opportunities, contact Beth Sheldahl, Spectrum Emergency Care, 6275 Lehman Dr, Ste C202, Colorado Springs, CO 80918; 1 (800) 525-3681; (303) 590-1755.

### PHYSICIANS WANTED

## SAN FRANCISCO

The San Francisco General Hospital AIDS Activities Division of the Department of Medicine of the University of California, San Francisco, is seeking applicants at the Assistant Clinical Professor level. Applicants should have completed a residency in Internal Medicine and be certified by the American Board of Internal Medicine. Additionally, applicants should have received post-residency training in General Internal Medicine or in a subspecialty relevant to AIDS such as Medical Oncology, Infectious Disease or Clinical Epidemiology. The individuals hired will be responsible for the care of AIDS patients, teaching on all levels, and are expected to participate actively in division research activities. Outpatient care is expected to be based in the SFGH AIDS Clinic. Inpatient care will be conducted at SFGH. Applicants should have demonstrated excellence in providing AIDS patient care and in medical teaching. Please submit current CV and three letters of reference to **Paul Volberding, MD, Search Committee Chair, AIDS Activities Division, Building 80, Ward 84, San Francisco General Hospital, 995 Potrero Ave, San Francisco, CA 94110.**

UCSF is an Equal Opportunity/Affirmative Action Employer.

**CALIFORNIA, SAN FRANCISCO BAY AREA.** A leading HMO near San Francisco, California is seeking Board prepared/certified physicians to staff a busy, urban, full-service Emergency Department. Kaiser Permanente is a large, pre-paid Health Maintenance Organization offering a competitive salary, job security, shareholder status, and generous benefits including health care, life insurance, disability insurance, sick leave, and educational leave. Please address all inquiries to Hans P. Odsen, MD, Chief, Emergency Department, Kaiser Permanente Medical Center, 1200 El Camino Real, South San Francisco, CA 94080; (415) 742-2513 or 2514.

**DERMATOLOGIST.** An expanding HMO in San Francisco is seeking a BC Dermatologist for a part-time position. Outpatient and inpatient responsibilities for consultations by referral. Send CV to Medical Director, PO Box 7883, San Francisco, CA 94120-9889.

**WASHINGTON STATE, SEATTLE AREA.** Multispecialty group of 9 physicians seeking OB/GYN and Family Practice physician for rapidly growing low risk practice. Community hospital located approximately 10 blocks from Clinic. Enumclaw is a family-oriented community, 50 miles from urban area and 60 minutes from outstanding ski resort. Send CV to Barbara Bellack, Clinic Manager, 3021 Griffin Ave, Enumclaw, WA 98022.

**CHIEF OF PEDIATRICS.** Natividad Medical Center, a University of California, San Francisco affiliated hospital, located in beautiful Monterey County, is seeking a BC/BE Pediatrician. Preference given to physician with Chief Residency or subspecialty experience. Natividad sponsors a family practice residency program with 18 residents. Salary range from $73,000 to $78,000 depending upon qualifications with excellent benefit package. Natividad Medical Center is an Affirmative Action Equal Opportunity Employer. For further information, please mail CV or contact Richard McClurkin, Personnel Officer/Search Board Leader, PO Box 8-1611, Salinas, CA 93912-1611; (408) 757-0581.

**FAMILY PRACTITIONER.** Full-time BE/BC FP for growing multispecialty group in sunny California. Some Spanish helpful. First year compensation, benefits, and malpractice. Partnership potential second year. Send CV to Number 29, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

*(Continued on Page 782)*

# Un-switch-ables

Patients and physicians alike prefer

## Transderm-Nitro®

nitroglycerin

Over half a billion* patches prescribed in the U.S. since 1982

The only patch with a rate-limiting membrane

Familiar, distinctive tan color and unique shape recognized by patients everywhere

**There's no substitute for experience**

C I B A

(See Brief Summary of Prescribing Information on the next page.)

*Data on file, CIBA Pharmaceutical Co.

629-7750-A

# Transderm-Nitro®
## nitroglycerin
## Transdermal Therapeutic System

*BRIEF SUMMARY (FOR FULL PRESCRIBING INFORMATION, SEE PACKAGE INSERT)*

**INDICATIONS AND USAGE**
This drug product has been conditionally approved by the FDA for the prevention and treatment of angina pectoris due to coronary artery disease. The conditional approval reflects a determination that the drug may be marketed while further investigation of its effectiveness is undertaken. A final evaluation of the effectiveness of the product will be announced by the FDA.

**CONTRAINDICATIONS**
Intolerance of organic nitrate drugs, marked anemia, increased intraocular pressure or increased intracranial pressure.

**WARNINGS**
In patients with acute myocardial infarction or congestive heart failure, Transderm-Nitro system should be used under careful clinical and/or hemodynamic monitoring.
In terminating treatment of anginal patients, both the dosage and frequency of application must be gradually reduced over a period of 4 to 6 weeks to prevent sudden withdrawal reactions, which are characteristic of all vasodilators in the nitroglycerin class.
Transdermal nitroglycerin systems should be removed before attempting defibrillation or cardioversion because of the potential for altered electrical conductivity which may enhance the possibility of arcing, a phenomenon associated with the use of defibrillators.

**PRECAUTIONS**
Symptoms of hypotension, such as faintness, weakness or dizziness, particularly orthostatic hypotension may be due to overdosage. When these symptoms occur, the dosage should be reduced or use of the product discontinued.
Transderm-Nitro system is not intended for immediate relief of anginal attacks. For this purpose occasional use of the sublingual preparations may be necessary.

**ADVERSE REACTIONS**
Transient headaches are the most common side effect, especially when higher doses of the drug are used. These headaches should be treated with mild analgesics while Transderm-Nitro therapy is continued. When such headaches are unresponsive to treatment, the nitroglycerin dosage should be reduced or use of the product discontinued.
Adverse reactions reported less frequently include hypotension, increased heart rate, faintness, flushing, dizziness, nausea and vomiting. These symptoms are attributable to the known pharmacologic effects of nitroglycerin, but may be symptoms of overdosage. When they persist the dose should be reduced or use of the product discontinued. In some patients, dermatitis may occur.

**DOSAGE AND ADMINISTRATION**
Therapy should be initiated with application of one Transderm-Nitro 5 system to the desired area of skin. Many patients prefer the chest; if hair is likely to interfere with system adhesion or removal, it can be clipped prior to placement of the system. Each system is designed to remain in place for 24 hours, and each successive application should be to a different skin area. Transderm-Nitro system should not be applied to the distal parts of the extremities.
The usual dosage is one Transderm-Nitro 5 system every 24 hours. Some patients, however, may require the Transderm-Nitro 10 system. If a single Transderm-Nitro 5 system fails to provide adequate clinical response, the patient should be instructed to remove it and apply either two Transderm-Nitro 5 systems or one Transderm-Nitro 10 system. More systems may be added as indicated by continued careful monitoring of clinical response. The Transderm-Nitro 2.5 system is useful principally for decreasing the dosage gradually, though it may provide adequate therapy for some patients when used alone.
The optimal dosage should be selected based upon the clinical response, side effects, and the effects of therapy upon blood pressure. The greatest attainable decrease in resting blood pressure that is not associated with clinical symptoms of hypotension especially during orthostasis indicates the optimal dosage. To decrease adverse reactions, the size and/or number of systems should be tailored to the individual patient's needs.
Do not store above 86°F (30°C).

**PATIENT INSTRUCTIONS FOR APPLICATIONS**
A patient leaflet is supplied with the systems.

**HOW SUPPLIED**

| Transderm-Nitro System Rated Release *in vivo* | Total Nitroglycerin in System | System Size | Carton Size |
|---|---|---|---|
| 2.5 mg/24 hr | 12.5 mg | 5 $cm^2$ | 30 Systems (NDC 0083-2025-26)<br>*100 Systems (NDC 0083-2025-30) |
| 5 mg/24 hr | 25 mg | 10 $cm^2$ | 30 Systems (NDC 0083-2105-26)<br>*100 Systems (NDC 0083-2105-30) |
| 10 mg/24 hr | 50 mg | 20 $cm^2$ | 30 Systems (NDC 0083-2110-26)<br>*100 Systems (NDC 0083-2110-30) |
| 15 mg/24 hr | 75 mg | 30 $cm^2$ | 30 Systems (NDC 0083-2115-26)<br>*100 Systems (NDC 0083-2115-30) |

*Hospital Pack 100's

C85-35 (Rev. 11/85)

**Dist. by:**
**CIBA Pharmaceutical Company**
**Division of CIBA-GEIGY Corporation**
**Summit, New Jersey 07901**

All transdermal nitroglycerin products are being marketed pending final evaluation of effectiveness by the FDA.

© 1986, CIBA. 629-7750-A

C I B A


# In Memoriam

## *California Medical Association*

AMANO, FUMIKO Y., Los Angeles. Died Jan 8, 1987, aged 83. Graduate of Yale University School of Medicine, New Haven, Connecticut, 1929. Licensed in California in 1930. Dr Amano was a member of the Los Angeles County Medical Association.

❧

ASH, DONALD W., Oakland. Died Apr 7, 1987, aged 74. Graduate of Tufts College Medical School, Boston, 1941. Licensed in California in 1944. Dr Ash was a member of the Alameda-Contra Costa Medical Association.

❧

BERKOVE, SADIE VOLOVICK, Oakland. Died Jan 23, 1987, aged 79. Graduate of University of California, San Francisco, 1931. Licensed in California in 1931. Dr Berkove was a member of the Alameda-Contra Costa Medical Association.

❧

BJORNSON, LYALL A., Oxnard. Died Mar 3, 1987, aged 45. Graduate of Bowman Gray School of Medicine, Winston-Salem, North Carolina, 1966. Licensed in California in 1969. Dr Bjornson was a member of the Ventura County Medical Society.

❧

CALVIN, GEORGE, Walnut Creek. Died Mar 13, 1987, aged 86. Graduate of University of Pennsylvania School of Medicine, Philadelphia, 1926. Licensed in California in 1929. Dr Calvin was a member of the Alameda-Contra Costa Medical Association.

❧

CARLSON, CARL O., San Jose. Died Mar 20, 1987, aged 74. Graduate of Stanford University School of Medicine, 1939. Licensed in California in 1939. Dr Carlson was a member of the Santa Clara County Medical Society.

❧

DICKSON, JAMES D. Died Jan 1987, aged 72. Graduate of Tulane University School of Medicine, New Orleans, 1938. Licensed in California in 1943. Dr Dickson was a member of the Shasta-Trinity County Medical Society.

❧

DODSON, JERRY G., La Habra. Died Feb 15, 1987, aged 58. Graduate of Johns Hopkins University School of Medicine, Baltimore, 1955. Licensed in California in 1963. Dr Dodson was a member of the Orange County Medical Association.

❧

FIELDS, JACK, North Hollywood. Died Feb 2, 1987, aged 76. Graduate of University of Illinois, Chicago, 1937. Licensed in California in 1947. Dr Fields was a member of the Los Angeles County Medical Association.

❧

FUNK, JOHN W., Riverside. Died Mar 13, 1987, aged 72. Graduate of Indiana University School of Medicine, Indianapolis, 1943. Dr Funk was a member of the Riverside County Medical Association.

❧

GAEDE, MENNO S., Reedley. Died Feb 8, 1987, aged 85. Graduate of University of Kansas School of Medicine, Kansas City, 1928. Licensed in California in 1930. Dr Gaede was a member of the Fresno-Madera Medical Society.

❧

GRONHOVD, GILBERT O., Anaheim. Died Mar 15, 1987, aged 88. Graduate of Rush Medical College, Chicago, 1931. Licensed in California in 1932. Dr Gronhovd was a member of the Los Angeles County Medical Association.

HACKLEY, ROGER W., Oakland. Died Apr 3, 1987, aged 74. Graduate of University of California, 1939. Licensed in California in 1939. Dr Hackley was a member of the Alameda-Contra Costa Medical Association.

❧

HARMON, ELLIS D., San Francisco. Died Feb 9, 1987, aged 89. Graduate of University of California, San Francisco, 1929. Licensed in California in 1929. Dr Harmon was a member of the San Francisco Medical Society.

❧

HARVEY, BERNARD J., Pomona. Died Mar 27, 1987, aged 76. Graduate of University of Nebraska College of Medicine, Omaha, 1935. Licensed in California in 1946. Dr Harvey was a member of the Los Angeles County Medical Association.

❧

HICKMAN, KYRMEL L., Fresno. Died Jan 22, 1987, aged 77. Graduate of University of California, Irvine. Dr Hickman was a member of the Fresno-Madera Medical Society.

❧

HINES, PHILLIP ROGER, Vallejo. Died Mar 16, 1987, aged 36. Graduate of Medical College of Ohio at Toledo, 1976. Licensed in California in 1978. Dr Hines was a member of the Solano County Medical Society.

❧

JACKSON, LETA B., Sacramento. Died Nov 27, 1986, aged 84. Graduate of University of California, Irvine. Dr Jackson was a member of the Sacramento-El Dorado Medical Society.

❧

KESTERSON, ROBERT L. Died Mar 26, 1987, aged 71. Graduate of University of Louisville, 1940. Licensed in California in 1941. Dr Kesterson was a member of the Alameda-Contra Costa Medical Association.

❧

LEONARD, NOBLE D., San Francisco. Died Dec 17, 1986, aged 84. Graduate of University of Michigan Medical School, Ann Arbor, 1929. Licensed in California in 1948. Dr Leonard was a member of the San Francisco Medical Society.

❧

LEVIN, SIDNEY, San Francisco. Died Mar 18, 1987, aged 59. Graduate of University of California, San Francisco, 1950. Licensed in California in 1950. Dr Levin was a member of the San Francisco Medical Society.

❧

LOUIE, STANLEY, San Francisco. Died Mar 24, 1987, aged 78. Graduate of Harvard Medical School, Boston, 1937. Licensed in California in 1939. Dr Louie was a member of the San Francisco Medical Society.

❧

LUKENS, JAMES T., Carmichael. Died Mar 12, 1987, aged 62. Graduate of University of Maryland, Baltimore, 1949. Licensed in California in 1956. Dr Lukens was a member of the Sacramento-El Dorado Medical Society.

❧

MAHER, FRANK M., San Jose. Died Feb 25, 1986, aged 70. Graduate of Northwestern University Medical School, Chicago, 1944. Dr Maher was a member of the Santa Clara County Medical Society.

*(Continued on Page 796)*

# When considering professional liability protection, choose the Mutual Protection Trust

| Specialty | 1987 CAP/MPT Estimated Cost* |
|---|---|
| Allergy | $ 2,371 |
| Anesthesia | 15,840 |
| Cardiology with invasive vascular procedures | 10,924 |
| Cardiology — no invasive vascular procedures | 5,222 |
| Dermatology — no radiation or hair transplants | 5,222 |
| Gastroenterology with endoscopy and ERCP, board certified | 8,073 |
| Family Practice — no surgery | 5,222 |
| Family Practice — minor surgery or assisting at surgery | 8,073 |
| Family Practice — major surgery | 17,905 |
| General Surgery | 17,905 |
| Internal Medicine with invasive vascular procedures | 10,924 |
| Internal Medicine — no invasive vascular procedures | 5,222 |
| Neurology — no electro-convulsive therapy | 2,371 |
| Ophthalmology with surgery or laser | 8,073 |
| Orthopedics with spinal surgery | 22,035 |
| Orthopedics — no spinal surgery | 19,970 |
| Otolaryngology — doing plastic surgery, board certified | 17,905 |
| Pediatrics — General | 2,371 |
| Pediatrics — General, with invasive vascular procedures | 10,924 |
| Plastic Surgery, board certified | 17,905 |
| Psychiatry — no electro-convulsive therapy | 2,371 |
| Radiology — diagnostic, no coronary angiography | 5,222 |
| Radiology — including coronary angiography | 10,924 |
| Urology | 13,775 |

*These rates include dues and assessments for a CAP/MPT member with 50 or more months of membership or retroactive coverage (matured rate). CAP/MPT offers coverage limits of $1 million per occurrence with an aggregate of $3 million per year.

**CAP/MPT offers:**

- **EXPERIENCE: The oldest California Trust providing professional liability protection**
- QUALITY: Stringent screening process — each member has a voice in the selection of new members
- **SAVINGS: Compare our cost with other experienced providers of malpractice protection**
- REINSURANCE: Limits assessment exposure
- **LOSS PREVENTION PROGRAMS: Education reduces malpractice risk**
- RETROACTIVE COVERAGE: For qualified members

In addition to dues and assessments, CAP/MPT members pay a one-time initial trust contribution based on risk classification. This can be paid in installments and is refundable under the terms of the MPT Agreement.

**MUTUAL PROTECTION TRUST**

**Cooperative of American Physicians, Inc.**

P.O. Box 76998
Los Angeles, CA 90076-0998

## (800) 252-7706

Call to find out what your cost would be with MPT

# "I gave up private practice ... but I didn't give up practicing."

What a difference... enjoy practicing medicine and let FHP take care of the business end. No worrying about administrative hassles, staffing problems, costly insurance... instead, with scheduled work hours, you're free to enjoy the Southern California lifestyle. Plus, as an FHP physician, you'll receive generous paid vacation, complete malpractice coverage, an excellent retirement plan and many other benefits including, of course, an outstanding salary with tax-deferred compensation plan.

FHP is a well-established and progressive HMO and we enjoy proximity to and support of several university programs in the area. Our steady growth coupled with the opening of our own 125-bed hospital last year, has created career opportunities for BC/BE Primary Care Physicians. For more information about joining our progressive team of professionals, please write or call (800) 446-2255, or (800) 336-2255 within California.

FHP

**Professional Staffing, Dept. 45**
**9900 Talbert Avenue**
**Fountain Valley, CA 92708**


*(Continued from Page 778)*

## PHYSICIANS WANTED

### SOUTHERN CALIFORNIA

Enjoy professional challenge and growth with a successful and expanding HMO in Southern California. CIGNA Healthplans of California is seeking Specialists and Primary Care physicians committed to concepts of prevention and health maintenance to join our facilities in Los Angeles and Orange Counties. We offer an excellent compensation and benefits package including profit sharing. For consideration, please forward CV to:

**Director/Physician Recruitment**
**CIGNA Healthplans of California**
**505 N. Brand Blvd, Suite 400-49**
**Glendale, CA 91203**

**ORTHOPEDIC SURGEON.** Natividad Medical Center, a University of California, San Francisco affiliated hospital, located in beautiful Monterey County, is recruiting an Orthopedic Surgeon. This position combines teaching and practice. The hospital sponsors a family practice residency program with 18 residents and has a very active trauma service with a regional paramedic base station. An attractive base salary with fee-for-service incentive option is negotiable. Natividad Medical Center is an Affirmative Action Equal Opportunity Employer. For further information, please mail CV or contact: Richard McClurkin, Personnel Officer/Search Board Leader, PO Box 8-1611, Salinas, CA 93912-1611; (408) 757-0581.

**EXCELLENT TEXAS OPPORTUNITIES.** ENT, Family Practitioner, General Practitioner, General Surgeon, Internal Medicine, OB/GYN person, to practice in one of several lake area communities, in the beautiful Piney Woods area of east Texas. Enjoy boating, fishing, hunting year 'round. Excellent quality of life, first year guarantee, etc. Reply with CV to Medical Support Services, Armando L. Frezza, 11509 Quarter Horse Trail, Austin, TX 78750; (512) 331-4164.

## PHYSICIANS WANTED

**PYSCHIATRIST—BC/BE** for northern California practice oriented towards clinical, occupational and evaluative medicine; qualified applicants will have EMG/NCS, EEG experience, be familiar with med-legal environment and seek a growth oriented opportunity; send current CV, letter of interest and compensation requirements to Box 164, 1550 California St, Ste 6, San Francisco, CA 94109.

**MEDICAL DIRECTOR** sought for women's nonprofit clinic in San Francisco. Responsibilities 80% clinical, 20% administrative. Emphases of the clinic include preventative health, outpatient gynecology, lesbian health care. Job is part-time, salary negotiable. Send CV with letter to Lyon-Martin Clinic, 2480 Mission St, #214, San Francisco, CA 94110. Deadline: June 30, 1987.

**OREGON.** Emergency department Medical Director and full-time Staff Physician are needed at client hospital located in community on the Columbia River in north central Oregon. Full service community hospital with moderate volume emergency department. Guaranteed rate of reimbursement, occurrence malpractice insurance coverage, CME allowance, reimbursement of professional dues, plus directors receive paid health benefits which include dependents. For additional information on this opportunity, contact Bill Salmo, Spectrum Emergency Care, 6275 Lehman Dr, Ste C202, Colorado Springs, CO 80918; 1 (800) 525-3681; (303) 590-1755.

**MD NEEDS**—OB/GYN and IM or IM/Oncologist needed for a multispecialty group practice in Helena, Montana. Capital of state, population 30,000-35,000, small private college, close to Rocky Mountains with fishing, hunting and outdoor sports. Midway between Glacier and Yellowstone Parks. Reply to Dan B. Smelko, Helena Medical Clinic, PC, 1930 9th Ave, Helena, MT 59601.

## PHYSICIANS WANTED

**SALT LAKE AREA.** General Practitioner needed for new, fully-equipped facility. Excellent salary—benefit package, plus percentage. Enjoy outdoor recreation, skiing, hunting, fishing, as well as cosmopolitan living. Reply to Number 34, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

**INTERNIST NEEDED FULL-TIME.** Primary Care position for Board certified Internist is now available with a growing San Francisco Health Plan. The position includes both inpatient and outpatient responsibilities. Send CV to Medical Director, French Health Plan, 4131 Geary Blvd, San Francisco, CA 94118.

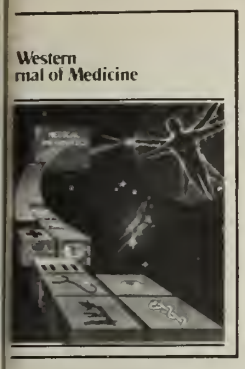
**ORTHOPEDIC SURGEON.** Full-time Orthopedic Surgeon to join growing multispecialty group in sunny California. Salary, incentive, malpractice and benefits. Great potential for right physician. Individual ownership. Send CV to Number 30, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

**INTERNIST**—Growing Long Beach, California industrial clinic seeks Internist to evaluate and treat Workers' Compensation patients. Position requires good communication skills and good patient rapport. No nights or weekends. Excellent benefits. Contact R. Unitan, 4237 Atlantic Ave, Long Beach, CA 90807; (213) 424-0423.

**INTERNAL MEDICINE.** Full-time BE/BC active Internist for multispecialty group in sunny California. Office/hospital and consult practice. Spanish a plus. Salary, benefits, and malpractice. Potential for partnership second year. Send CV to Number 31, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

*(Continued on Page 789)*

# SPECIAL ISSUES

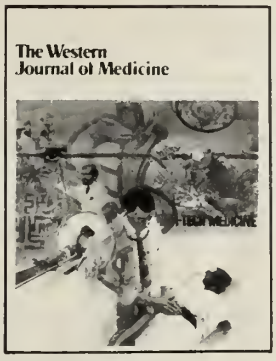



## Medical Informatics

I would suggest that the computer in its relation to medicine is analogous to that of the microscope in the last century. . . . The analogous role that I believe the computer is now taking on is also that of a breakthrough tool—one enabling us to explore and better understand the informational and cognitive foundations of medicine. Its application to the classification and retrieval of data and to the management of information will result in a deeper insight into the structure of medical information and knowledge itself.

*—Marsden S. Blois, PhD, MD*

| ıtity | Per Copy* |
|---|---|
| gle copy | $4.50 |
| 10 | 4.00 |
| o 50 | 3.50 |
| re than 50 | 3.00 |

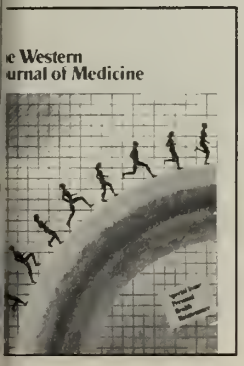



## High-Tech Medicine

Progress in medical science seems to come in rushes. There are long periods of time during which we mainly fine-tune the status quo: third-generation drugs, better optics for endoscopes, more accurate assays, rapid development of x-ray film and so forth. Then, out of nowhere, a surge of new discoveries whose potential applications to medical practice seem limitless takes our breath away. We are now in such an epoch. Powerful and precise lasers. Almost unbelievable organ transplantation. Complex and uniquely informative magnetic resonance imaging and positron emission tomography. Exquisitely specific monoclonal antibodies. And the immense potential of modern molecular biology. This rush of new advances, collapsed into such a brief period of time, boggles the mind.

*—R. Paul Robertson, MD*

| Quantity | Per Copy* |
|---|---|
| Single copy | $4.50 |
| 2 to 10 | 4.00 |
| 11 to 50 | 3.50 |
| More than 50 | 3.00 |

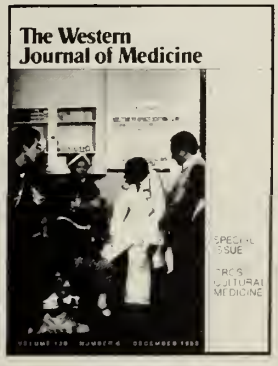



## Personal Health Maintenance

The goal of this special issue is to provide an authoritative, current guide to disease prevention and health promotion. The contributors are distinguished experts in public health, epidemiology and clinical medicine.

*—John H. Holbrook, MD*

| ıntity | Per Copy* |
|---|---|
| ıgle copy | $4.50 |
| ) 10 | 4.00 |
| to 50 | 3.50 |
| ıre than 50 | 3.00 |




## Cross-cultural Medicine

**Reprinted as a book because of extraordinary demand**

The barriers may be great indeed when an American-trained physician undertakes to treat a patient from another ethnic or religious background. Too little attention has been given to developing better or even adequate communication across all these different cultures. The subject is of worldwide social, economic and political importance, and on a more individual and personal basis it is important in patient care.

*—Malcolm S. M. Watts, MD*

| Quantity | Per Copy* |
|---|---|
| Single copy | $6.50 |
| 2 to 10 | 6.00 |
| 11 to 50 | 5.50 |
| More than 50 | 5.00 |

WJ6/87

## ORDER FORM

*Note: Domestic postage and handling included. Please add California & local sales tax where applicable. Foreign postage additional.

**Please send me:**

___ copies of Medical Informatics
___ copies of High-Tech Medicine
___ copies of Personal Health Maintenance
___ copies of Cross-Cultural Medicine

**Payment must accompany order.**

Total amount enclosed $_____

Name _____

Address _____

City/State/Zip _____

Charge my account ☐ VISA ☐ MASTERCARD

#_____ Exp. date _____

Signature _____

**Mail to:** Circulation Department, The Western Journal of Medicine
P.O. Box 7602, San Francisco, CA 94120-7602

CONTINUING MEDICAL EDUCATION

(Continued from Page 688)

July 17-18—**Coronary Heart Disease: Current Concepts.** Medical Education Resources at Sheraton Hotel, Anaheim. Fri-Sat. 11 hrs. $295. Contact: Debbie Wilderson, 5808 S Rapp St, Ste 202, Littleton, CO 80120. (800) 421-3756.

July 31-August 1—**Arrhythmias: Interpretation, Diagnosis, and Management.** Medical Education Resources at Harvey's Hotel, Lake Tahoe, Nevada. Fri-Sat. 11 hrs. $295. Contact: Debbie Wilderson, 5808 S Rapp St, Ste 202, Littleton, CO 80120. (800) 421-3756.

August 2-7—**Current Concepts in Cardiology.** UCD at Hyatt Lake Tahoe, Incline Village, Nevada. Sun-Fri. Contact: UCD.

August 7-8—**Coronary Heart Disease: Current Concepts.** Medical Education Resources at Doubletree Inn, Monterey. Fri-Sat. 11 hrs. $295. Contact: Debbie Wilderson, 5808 S Rapp St, Ste 202, Littleton, CO 80120. (800) 421-3756 or (303) 798-9682.

September 12—**57th Annual Physicians' Postgraduate Symposium on Cardiovascular Disease.** American Heart Association, San Francisco at Cathedral Hill Hotel, San Francisco. Sat. 9 hrs. $100. Contact: AHA, 42 Powell St, San Francisco 94102. (415) 433-2273

September 17-18—**Optimal Coronary Revascularization.** Santa Barbara Medical Foundation Clinic, Sansum Medical Clinic and Santa Barbara Cottage Hospital at Red Lion Resort Hotel, Santa Barbara. Thurs-Fri. 14 hrs. $275. Contact: Nomi Feldman, 3770 Tansy, San Diego 92121. (619) 453-6222.

September 18-20—**Diagnosis and Management of Respiratory Diseases.** Medical Education Resources at Tropicana Hotel, Las Vegas, Nevada. Fri-Sun. 13 hrs. $295. Contact: Medical Education Resources, 5808 S Rapp St, Ste 202, Littleton, CO 80120. (800) 421-3756.

October 15-17—**11th Annual Seminar: Cardiology Update 1987.** American College of Cardiology at Quail Lodge, Carmel. Thurs-Sat. Contact: Mary Anne McInerny, ACC, 9111 Old Georgetown Rd, Bethesda, MD 20814. (301) 897-5400.

October 15-17—**Recent Advances in Pulmonary and Critical Care Medicine.** UCSF at Hyatt on Union Square, San Francisco. Thurs-Sat. 15 hrs. $365. Contact: UCSF.

October 30-31—**Coronary Heart Disease.** Medical Education Resources at Las Vegas Hilton Hotel, Nevada. Fri-Sat. 11 hrs. $295. Contact: Medical Education Resources, 5808 S Rapp St, Ste 202, Littleton, CO 80120. (800) 421-3756.

November 13-14—**Arrhythmias: Interpretation, Diagnosis and Management.** Medical Education Resources at Hilton Hotel, San Francisco. Fri-Sat. 11 hrs. $295. Contact: Medical Education Resources, 5808 S Rapp St, Ste 202, Littleton, CO 80120. (800) 421-3756.

November 14—**16th Annual Cardiology Symposium.** Fresno Community Hospital at Center Plaza Hotel, Fresno. Sat. Contact: Joann Ellis, Fresno Community Hospital, PO Box 1232, Fresno 93715. (209) 442-3936.

## DERMATOLOGY

August 13-15—**Problems of the Aging Skin.** STAN at Hyatt Rickeys Hotel, Palo Alto. Thurs-Sat. Contact: STAN.

August 14-15—**Cryostat and Microscopically Controlled Surgical Workshop.** UCSD. Fri-Sat. 15 hrs. Contact: Daniel E. Gormley, MD, Director, 412 W Carroll, Glendora 91740. (818) 963-7684.

October 24-25—**16th Annual Mycology Review.** STAN at STAN. Sat-Sun. Contact: STAN.

## EMERGENCY MEDICINE

June 22-26—**Postgraduate Institute for Emergency and Primary Care Physicians, Symposium III and Advanced Emergency Procedures Lab.** UCSD at Hanalei Hotel, San Diego. Mon-Fri. 32 hrs. $325-440. Contact: UCSD.

June 25-28—**Wilderness Emergency Care.** Superior California Medical Education Council at Lava Creek Fishing Lodge, Fall River Mills. Thurs-Sun. 6 hrs. Contact: J. Bear Co, PO Box 117, Burney 96013. (916) 335-3388.

July 24-26—**Advanced Cardiac Life Support.** CPR Seminars at Ralph K. Davies Medical Center. San Franicsco. Fri-Sun. Contact: CPR Seminars, 833 Market St, Ste 421, San Francisco 94103. (415) 543-7282.

August 12-16—**Wilderness Medicine: 1987.** Siskiyou General Hospital at Northstar, Tahoe Resort. Wed-Sun. 20 hrs. $395. Contact: Jackie Silva, PO Box 321, Yreka 96097. (916) 842-6848.

August 17-21—**Postgraduate Institute for Emergency and Primary Care Physicians, Symposium II and Advanced Emergency Procedures Lab.** UCSD at UCSD. Mon-Fri. 32 hrs. $325-440. Contact: UCSD.

August 23-28—**New Advances in Internal Medicine.** UCD at Hyatt Monterey. Sun-Fri. Contact: UCD.

August 31-September 4—**Topics in Emergency Medicine.** UCSF at Holiday Inn Union Square, San Francisco. Mon-Fri. 31 hrs. $420. Contact: UCSF.

October 16-17—**2nd Annual Symposium on Advanced Pediatric Emergency Medicine and Trauma.** UCI at Long Beach Airport Marriott Hotel. Fri-Sat. Contact: UCI.

October 23-25—**Advanced Cardiac Life Support.** CPR Seminars at Ralph K. Davies Medical Center, San Francisco. Fri-Sun. Contact: CPR Seminars, 833 Market St, Ste 421, San Francisco 94103. (415) 543-7282.

October 26-30—**Current Topics in Occupational Medicine.** UCSF at Cathedral Hill Hotel, San Francisco. Mon-Fri. 40 hrs. $550.

## INTERNAL MEDICINE

June 17-19—**Gastroenterology: Recent Developments in Theory and Practice.** UCSF at Hyatt on Union Square, San Francisco. Wed-Fri. 17 hrs. $375. Contact: UCSF.

June 22-26—**Advances in Internal Medicine.** UCSF at UCSF. Mon-Fri. 32 hrs. $440.

June 26—**Mucosal Injury, Esophageal Dysfunction, and Sleep Disorders.** Sequoia Hospital District, Redwood City. Fri. 7 hrs. $110. Contact: Daniel Liebowitz, MD, Sequoia Hospital, Whipple and Alameda, Redwood City 94062. (800) 345-0409.

July 18-20—**8th Annual Symposium on Laboratory and Clinical Aspects of Microbiological Diagnosis.** UCLA at Hyatt Regency Hotel, Monterey. Sat-Mon. 13 hrs. $175. Contact: UCLA.

August 23-28—**New Advances in Internal Medicine: Clinical Applications.** UCD at Hyatt Regency, Monterey. Sun-Fri. 23 hrs. $395. Contact: UCD.

October 10—**Clinical Update on Thromboembolic Disease and Anticoagulation.** UCD at Hilton Hotel, Sacramento. Sat. Contact: UCD.

## OB/GYN

June 25-26—**Advanced Fetal Heart Rate Monitoring.** UCI at Balboa Bay Club, Newport Beach. Thurs-Fri. 12 hrs. Contact: UCI.

June 30-July 5—**5th Annual Controversies in Obstetrics and Gynecology.** UCI at Mauna Kea Beach Resort, Hawaii. Tues-Sun. 22 hrs. Contact: UCI.

July 16-18—**Developmental Interventions in Neonatal Care.** American Academy of Pediatrics at San Francisco. Thurs-Sat. 17 hrs. Contact: Contemporary Forums, 530 La Gonda Way, Ste E, Danville 94526. (415) 820-2800.

October 16-18—**Advanced Fetal Heart Rate Monitoring.** UCI at Embassy Suites Hotel, Napa Valley. Fri-Sun. Contact: UCI.

## OPHTHALMOLOGY

August 1-8—**Ophthalmology.** USC at Mauna Kea, Hawaii. One week. 26 hrs. $525. Contact: USC.

August 30-Sept 2—**Under Pressure: Glaucoma 1987.** UCD at Hyatt Lake Tahoe, Incline Village, Nevada. Sun-Wed. Contact: UCD.

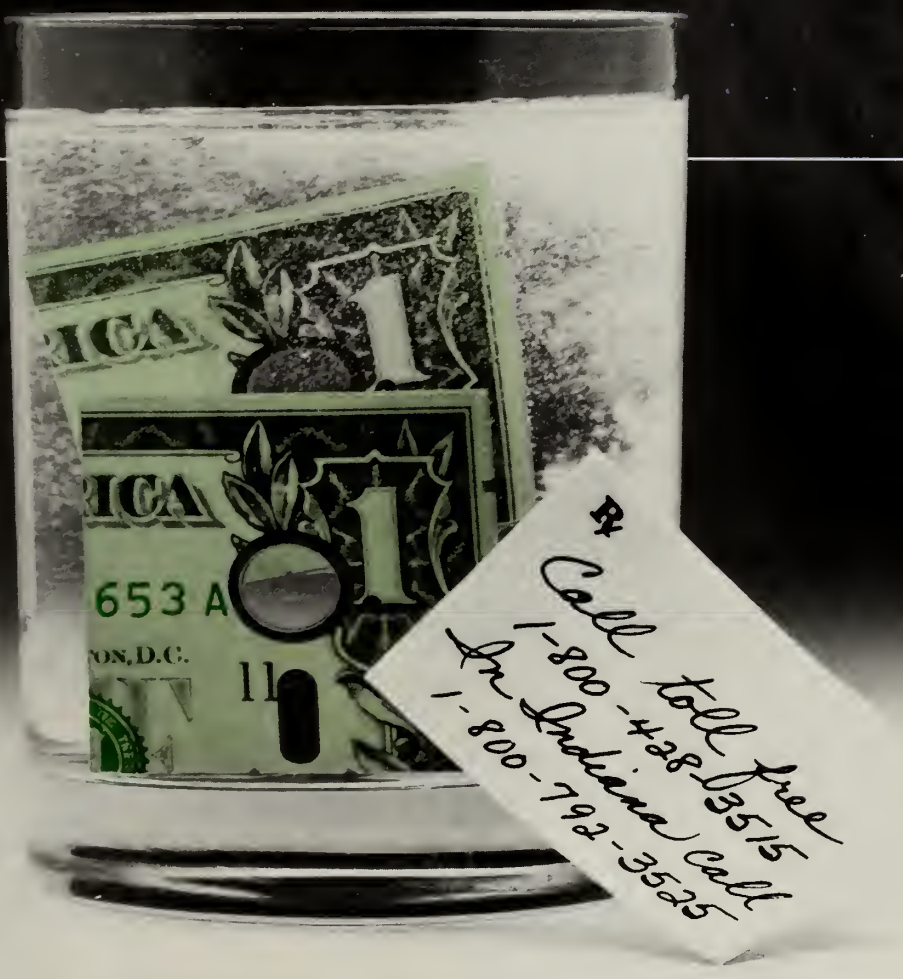
## PATHOLOGY

August 22-29—**7th Annual Symposium on Fine Needle Aspiration.** California Society of Pathologists and UCSF at Royal Lahaina Resort, Kaanapali Beach, Maui, Hawaii. One week. 24.5 hrs. Contact: UCSF.

October 3—**Fine Needle Aspiration Tutorial.** UCSF at UCSF. Sat. 7 hrs. $475. Contact: UCSF.

(Continued on Page 794)

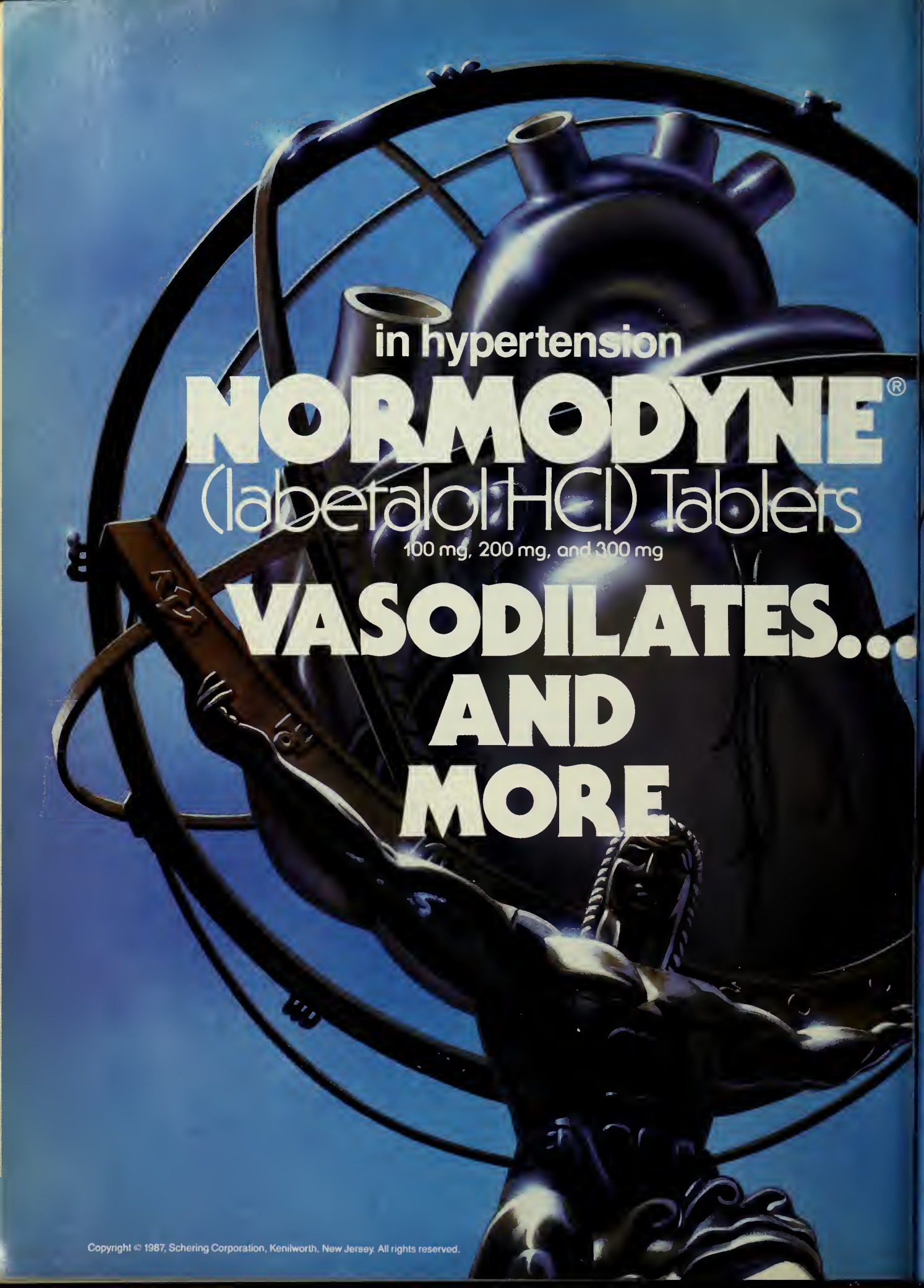
# fast acting



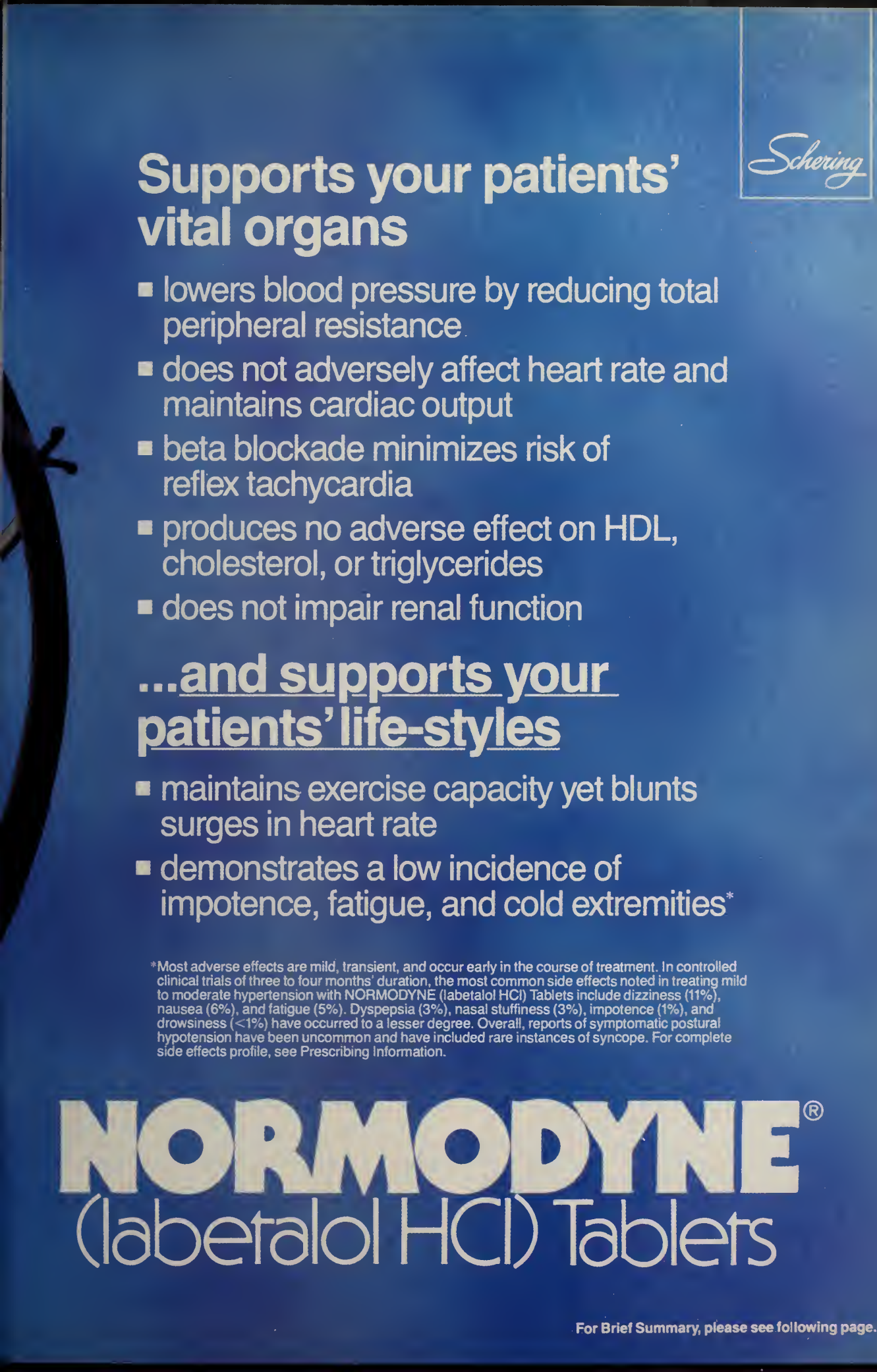

It's a headache. The pain of filing insurance claims. Typing the same names, same addresses, same billing numbers, same office procedures over and over. Translating diagnosis codes. Then waiting weeks for reimbursement. Sometimes you wonder if your claims ever got there at all. ☐ How do you get fast relief? With fast-acting electronic claims software from Physicians Practice Management. PPM software saves you time and trouble because your computer prepares the claims using accepted insurance company codes, and transmits them for you. At night. Unattended. Error-free. ☐ PPM systems run on any IBM®-PC™, XT™, AT™, PS/2™, or PC-compatibles. You can select from a family of products, starting with basic electronic claims for $89.95, and expand upwards to complete office management for less than $4,000. ☐ If claims processing is a pain in your patient service, it's easy to remedy the situation. Just call Physicians Practice Management. Specialists in automation for the medical profession.

The CLAIM*NET nationwide clearinghouse is approved for live electronic claims submission to Medicare and other insurance companies in the following states: AL, AK, AZ, CA, CO, DE, FL, GA, HI, ID, IL, IN, IA, KY, LA, ME, MD, MA, MI, MN, MS, MO, NV, NH, NJ, NM, NY, NC, ND, OH, OK, OR, PA, SC, TN, TX, VT, VA, WA, DC, WI, WV, WY.

**Physicians Practice Management**
1810 S. Lynhurst, Suite Q, Indianapolis, Indiana 46241
Software for the M.D.




Copyright © 1987, Schering Corporation, Kenilworth, New Jersey. All rights reserved.



Schering

# Supports your patients' vital organs

- lowers blood pressure by reducing total peripheral resistance
- does not adversely affect heart rate and maintains cardiac output
- beta blockade minimizes risk of reflex tachycardia
- produces no adverse effect on HDL, cholesterol, or triglycerides
- does not impair renal function

# ...and supports your patients' life-styles

- maintains exercise capacity yet blunts surges in heart rate
- demonstrates a low incidence of impotence, fatigue, and cold extremities*

*Most adverse effects are mild, transient, and occur early in the course of treatment. In controlled clinical trials of three to four months' duration, the most common side effects noted in treating mild to moderate hypertension with NORMODYNE (labetalol HCl) Tablets include dizziness (11%), nausea (6%), and fatigue (5%). Dyspepsia (3%), nasal stuffiness (3%), impotence (1%), and drowsiness (<1%) have occurred to a lesser degree. Overall, reports of symptomatic postural hypotension have been uncommon and have included rare instances of syncope. For complete side effects profile, see Prescribing Information.

# NORMODYNE®
## (labetalol HCl) Tablets

For Brief Summary, please see following page.

13071942-JBS

**PRODUCT INFORMATION**

# NORMODYNE®

**brand of labetalol hydrochloride**

## Tablets

BRIEF SUMMARY

### INDICATIONS AND USAGE

NORMODYNE (labetalol HCl) Tablets are indicated in the management of hypertension. NORMODYNE Tablets may be used alone or in combination with other antihypertensive agents, especially thiazide and loop diuretics.

### CONTRAINDICATIONS

NORMODYNE (labetalol HCl) Tablets are contraindicated in bronchial asthma, overt cardiac failure, greater than first degree heart block, cardiogenic shock, and severe bradycardia (see **WARNINGS**).

### WARNINGS

*Cardiac Failure* Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure. Beta blockade carries a potential hazard of further depressing myocardial contractility and precipitating more severe failure. Although beta-blockers should be avoided in overt congestive heart failure, if necessary, labetalol HCl can be used with caution in patients with a history of heart failure who are well-compensated. Congestive heart failure has been observed in patients receiving labetalol HCl. Labetalol HCl does not abolish the inotropic action of digitalis on heart muscle.

*In Patients Without a History of Cardiac Failure* In patients with latent cardiac insufficiency, continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or be given a diuretic, and the response observed closely. If cardiac failure continues, despite adequate digitalization and diuretic, NORMODYNE (labetalol HCl) therapy should be withdrawn (gradually if possible).

*Exacerbation of Ischemic Heart Disease Following Abrupt Withdrawal* Angina pectoris has not been reported upon labetalol HCl discontinuation. However, hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred after *abrupt* discontinuation of such therapy. When discontinuing chronically administered NORMODYNE (labetalol HCl), particularly in patients with ischemic heart disease, the dosage should be gradually reduced over a period of one to two weeks and the patient should be carefully monitored. If angina markedly worsens or acute coronary insufficiency develops, NORMODYNE (labetalol HCl) administration should be reinstituted promptly, at least temporarily, and other measures appropriate for the management of unstable angina should be taken. Patients should be warned against interruption or discontinuation of therapy without the physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue NORMODYNE (labetalol HCl) therapy abruptly even in patients treated only for hypertension.

**Nonallergic Bronchospasm (e.g., chronic bronchitis and emphysema) Patients with bronchospastic disease should, in general, not receive beta-blockers.** NORMODYNE may be used with caution, however, in patients who do not respond to, or cannot tolerate, other antihypertensive agents. It is prudent, if NORMODYNE is used, to use the smallest effective dose, so that inhibition of endogenous or exogenous beta-agonists is minimized.

*Pheochromocytoma* Labetalol HCl has been shown to be effective in lowering the blood pressure and relieving symptoms in patients with pheochromocytoma. However, paradoxical hypertensive responses have been reported in a few patients with this tumor; therefore, use caution when administering labetalol HCl to patients with pheochromocytoma.

*Diabetes Mellitus and Hypoglycemia* Beta-adrenergic blockade may prevent the appearance of premonitory signs and symptoms (e.g., tachycardia) of acute hypoglycemia. This is especially important with labile diabetics. Beta-blockade also reduces the release of insulin in response to hyperglycemia; it may therefore be necessary to adjust the dose of antidiabetic drugs.

*Major Surgery* The necessity or desirability of withdrawing beta-blocking therapy prior to major surgery is controversial. Protracted severe hypotension and difficulty in restarting or maintaining a heart beat have been reported with beta-blockers. The effect of labetalol HCl's alpha-adrenergic activity has not been evaluated in this setting.

A synergism between labetalol HCl and halothane anesthesia has been shown (see **Drug Interactions**).

### PRECAUTIONS

**General** *Impaired Hepatic Function* NORMODYNE (labetalol HCl) Tablets should be used with caution in patients with impaired hepatic function since metabolism of the drug may be diminished.

*Jaundice or Hepatic Dysfunction* On rare occasions, labetalol HCl has been associated with jaundice (both hepatic and cholestatic). It is therefore recommended that treatment with labetalol HCl be stopped immediately should a patient develop jaundice or laboratory evidence of liver injury. Both have been shown to be reversible on stopping therapy.

**Information for Patients**

As with all drugs with beta-blocking activity, certain advice to patients being treated with labetalol HCl is warranted. This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects. While no incident of the abrupt withdrawal phenomenon (exacerbation of angina pectoris) has been reported with labetalol HCl, dosing with NORMODYNE Tablets should not be interrupted or discontinued without a physician's advice. Patients being treated with NORMODYNE Tablets should consult a physician at any sign of impending cardiac failure. Also, transient scalp ringling may occur, usually when treatment with NORMODYNE Tablets is initiated (see **ADVERSE REACTIONS**).

**Laboratory Tests**

As with any new drug given over prolonged periods, laboratory parameters should be observed over regular intervals. In patients with concomitant illnesses, such as impaired renal function, appropriate tests should be done to monitor these conditions.

**Drug Interactions**

In one survey, 2.3% of patients taking labetalol HCl in combination with tricyclic antidepressants experienced tremor as compared to 0.7% reported to occur with labetalol HCl alone. The contribution of each of the treatments to this adverse reaction is unknown but the possibility of a drug interaction cannot be excluded.

Drugs possessing beta-blocking properties can blunt the bronchodilator effect of beta-receptor agonist drugs in patients with bronchospasm; therefore, doses greater than the normal anti-asthmatic dose of beta-agonist bronchodilator drugs may be required.

Cimetidine has been shown to increase the bioavailability of labetalol HCl. Since this could be explained either by enhanced absorption or by an alteration of hepatic metabolism of labetalol HCl, special care should be used in establishing the dose required for blood pressure control in such patients.

Synergism has been shown between halothane anesthesia and intravenously administered labetalol HCl. During controlled hypotensive anesthesia using labetalol HCl in association with halothane, high concentrations (3% or above) of halothane should not be used because the degree of hypotension will be increased and because of the possibility of a large reduction in cardiac output and an increase in central venous pressure. The anesthesiologist should be informed when a patient is receiving labetalol HCl.

Labetalol HCl blunts the reflex tachycardia produced by nitroglycerin without preventing its hypotensive effect. If labetalol HCl is used with nitroglycerin in patients with angina pectoris, additional antihypertensive effects may occur.

**Drug/Laboratory Test Interactions**

The presence of a metabolite of labetalol in the urine may result in falsely increased levels of urinary catecholamines when measured by a nonspecific trihydroxyindole (THI) reaction. In screening patients suspected of having a pheochromocytoma and being treated with labetalol HCl, specific radioenzymatic or high performance liquid chromatography assay techniques should be used to determine levels of catecholamines or their metabolites.

**Carcinogenesis, Mutagenesis, Impairment of Fertility**

Long-term oral dosing studies with labetalol HCl for 18 months in mice and for 2 years in rats showed no evidence of carcinogenesis. Studies with labetalol HCl, using dominant lethal assays in rats and mice, and exposing microorganisms according to modified Ames tests, showed no evidence of mutagenesis.

**Pregnancy Category C**

Teratogenic studies have been performed with labetalol in rats and rabbits at oral doses up to approximately 6 and 4 times the maximum recommended human dose (MRHD), respectively. No reproducible evidence of fetal malformations was observed. Increased fetal resorptions were seen in both species at doses approximating the MRHD. There are no adequate and well-controlled studies in pregnant women. Labetalol should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

**Nonteratogenic Effects**

Infants of mothers who were treated with labetalol HCl for hypertension during pregnancy did not appear to be adversely affected by the drug. Oral administration of labetalol to rats during late gestation through weaning at doses of 2 to 4 times the MRHD caused a decrease in neonatal survival.

**Labor and Delivery**

Labetalol HCl given to pregnant women with hypertension did not appear to affect the usual course of labor and delivery.

**Nursing Mothers**

Small amounts of labetalol (approximately 0.004% of the maternal dose) are excreted in human milk. Caution should be exercised when NORMODYNE Tablets are administered to a nursing woman.

**Pediatric Use**

Safety and effectiveness in children have not been established.

### ADVERSE REACTIONS

Most adverse effects are mild, transient and occur early in the course of treatment. In controlled clinical trials of 3 to 4 months duration, discontinuation of NORMODYNE (labetalol HCl) Tablets due to one or more adverse effects was required in 7% of all patients. In these same trials, beta-blocker control agents led to discontinuation in 8 to 10% of patients, and a centrally acting alpha-agonist in 30% of patients.

The incidence rates of adverse reactions listed in the following table were derived from multicenter controlled clinical trials, comparing labetalol HCl, placebo, metoprolol and propranolol, over treatment periods of 3 and 4 months. Where the frequency of adverse effects for labetalol HCl and placebo is similar, causal relationship is uncertain. The rates are based on adverse reactions considered probably drug-related by the investigator. If all reports are considered, the rates are somewhat higher (e.g., dizziness 20%, nausea 14%, fatigue 11%), but the overall conclusions are unchanged.

| | Labetalol HCl (N = 227) % | Placebo (N = 98) % | Propranolol (N = 84) % | Metoprolol (N = 49) % |
|---|---|---|---|---|
| Body as a whole | | | | |
| fatigue | 5 | 0 | 12 | 12 |
| asthenia | 1 | 1 | 1 | 0 |
| headache | 2 | 1 | 1 | 2 |
| Gastrointestinal | | | | |
| nausea | 6 | 1 | 1 | 2 |
| vomiting | <1 | 0 | 0 | 0 |
| dyspepsia | 3 | 1 | 1 | 0 |
| abdominal pain | 0 | 0 | 1 | 2 |
| diarrhea | <1 | 0 | 2 | 0 |
| taste distortion | 1 | 0 | 0 | 0 |
| Central and Peripheral Nervous Systems | | | | |
| dizziness | 11 | 3 | 4 | 4 |
| paresthesias | <1 | 0 | 0 | 0 |
| drowsiness | <1 | 2 | 2 | 2 |
| Autonomic Nervous System | | | | |
| nasal stuffiness | 3 | 0 | 0 | 0 |
| ejaculation failure | 2 | 0 | 0 | 0 |
| impotence | 1 | 0 | 1 | 3 |
| increased sweating | <1 | 0 | 0 | 0 |
| Cardiovascular | | | | |
| edema | 1 | 0 | 0 | 0 |
| postural hypotension | 1 | 0 | 0 | 0 |
| bradycardia | 0 | 0 | 5 | 12 |
| Respiratory | | | | |
| dyspnea | 2 | 0 | 1 | 2 |
| Skin | | | | |
| rash | 1 | 0 | 0 | 0 |
| Special Senses | | | | |
| vision abnormality | 1 | 0 | 0 | 0 |
| vertigo | 2 | 1 | 0 | 0 |

The adverse effects were reported spontaneously and are representative of the incidence of adverse effects that may be observed in a properly selected hypertensive patient population, i.e., a group excluding patients with bronchospastic disease, overt congestive heart failure, or other contraindications to beta-blocker therapy.

Clinical trials also included studies utilizing daily doses up to 2400 mg in more severely hypertensive patients. Certain of the side effects increased with increasing dose as shown in the table below which depicts the entire U.S. therapeutic trials data base for adverse reactions that are clearly or possibly dose related.

| Labetalol HCl Daily Dose (mg) | 200 | 300 | 400 | 600 |
|---|---|---|---|---|
| Number of Patients | 522 | 181 | 606 | 608 |
| Dizziness (%) | 2 | 3 | 3 | 3 |
| Fatigue | 2 | 1 | 4 | 4 |
| Nausea | <1 | 0 | 1 | 2 |
| Vomiting | 0 | 0 | <1 | <1 |
| Dyspepsia | 1 | 0 | 2 | 1 |
| Paresthesias | 2 | 0 | 2 | 2 |
| Nasal Stuffiness | 1 | 1 | 2 | 2 |
| Ejaculation Failure | 0 | 2 | 1 | 2 |
| Impotence | 1 | 1 | 1 | 1 |
| Edema | 1 | 0 | 1 | 1 |

| Labetalol HCl Daily Dose (mg) | 800 | 900 | 1200 | 1600 | 2400 |
|---|---|---|---|---|---|
| Number of Patients | 503 | 117 | 411 | 242 | 175 |
| Dizziness (%) | 5 | 1 | 9 | 13 | 16 |
| Fatigue | 5 | 3 | 7 | 6 | 10 |
| Nausea | 4 | 0 | 7 | 11 | 19 |
| Vomiting | <1 | 0 | 1 | 2 | 3 |
| Dyspepsia | 1 | 0 | 2 | 2 | 4 |
| Paresthesias | 1 | 1 | 2 | 5 | 5 |
| Nasal Stuffiness | 2 | 2 | 4 | 5 | 6 |
| Ejaculation Failure | 3 | 0 | 4 | 3 | 5 |
| Impotence | 2 | 4 | 3 | 4 | 3 |
| Edema | 1 | 0 | 1 | 2 | 2 |

In addition, a number of other less common adverse events have been reported in clinical trials or the literature:

*Cardiovascular* Postural hypotension, including rarely, syncope.

*Central and Peripheral Nervous Systems* Paresthesias, most frequently described as scalp tingling. In most cases, it was mild, transient and usually occurred at the beginning of treatment.

*Collagen Disorders* Systemic lupus erythematosus; positive antinuclear factor (ANF).

*Eyes* Dry eyes.

*Immunological System* Antimitochondrial antibodies.

*Liver and Biliary System* Cholestasis with or without jaundice.

*Musculo-Skeletal System* Muscle cramps; toxic myopathy.

*Respiratory System* Bronchospasm.

*Skin and Appendages* Rashes of various types, such as generalized maculo-papular; lichenoid; urticarial; bullous lichen planus; psoriaform; facial erythema; Peyronie's disease; reversible alopecia.

*Urinary System* Difficulty in micturition, including acute urinary bladder retention.

Following approval for marketing in the United Kingdom, a monitored release survey involving approximately 6,800 patients was conducted for further safety and efficacy evaluation of this product. Results of this survey indicate that the type, severity, and incidence of adverse effects were comparable to those cited above.

**Potential Adverse Effects**

In addition, other adverse effects not listed above have been reported with other beta-adrenergic blocking agents.

*Central Nervous System* Reversible mental depression progressing to catatonia; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

*Cardiovascular* Intensification of AV block. See **CONTRAINDICATIONS.**

*Allergic* Fever combined with aching and sore throat; laryngospasm; respiratory distress.

*Hematologic* Agranulocytosis; thrombocytopenic or nonthrombocytopenic purpura.

*Gastrointestinal* Mesenteric artery thrombosis; ischemic colitis.

The oculomucocutaneous syndrome associated with the beta-blocker practolol has not been reported with labetalol HCl.

**Clinical laboratory tests:** There have been reversible increases of serum transaminases in 4% of patients treated with labetalol HCl and tested, and more rarely, reversible increases in blood urea.

### OVERDOSAGE

Overdosage with NORMODYNE (labetalol HCl) Tablets causes excessive hypotension which is posture sensitive, and sometimes, excessive bradycardia. Patients should be laid supine and their legs raised if necessary to improve the blood supply to the brain. The following additional measures should be employed if necessary: *Excessive bradycardia* — administer atropine (3.0 mg). If there is no response to vagal blockade, administer isoproterenol cautiously. *Cardiac failure* — administer a digitalis glycoside and a diuretic. *Hypotension* — administer vasopressors, e.g., norepinephrine. There is pharmacological evidence that norepinephrine may be the drug of choice. *Bronchospasm* — administer a beta$_2$-stimulating agent and/or a theophylline preparation.

Gastric lavage or pharmacologically induced emesis (using syrup of ipecac) is useful for removal of the drug shortly after ingestion. Labetalol HCl can be removed from the general circulation by hemodialysis.

The oral $LD_{50}$ value of labetalol HCl in the mouse is approximately 600 mg/kg and in the rat is greater than 2 gm/kg. The intravenous $LD_{50}$ in these species is 50 to 60 mg/kg.

### DOSAGE AND ADMINISTRATION

DOSAGE MUST BE INDIVIDUALIZED. The recommended initial dose is 100 mg twice daily whether used alone or added to a diuretic regimen. After 2 or 3 days, using standing blood pressure as an indicator, dosage may be titrated in increments of 100 mg bid every 2 or 3 days. The usual maintenance dosage of labetalol HCl is between 200 and 400 mg twice daily.

Since the full antihypertensive effect of labetalol HCl is usually seen within the first one to three hours of the initial dose or dose increment, the assurance of a lack of an exaggerated hypotensive response can be clinically established in the office setting. The antihypertensive effects of continued dosing can be measured at subsequent visits, approximately 12 hours after a dose, to determine whether further titration is necessary.

Patients with severe hypertension may require from 1200 mg to 2400 mg per day, with or without thiazide diuretics. Should side effects (principally nausea or dizziness) occur with these doses administered bid, the same total daily dose administered three times daily may improve tolerability and facilitate further titration. Titration increments should not exceed 200 mg twice daily.

When a diuretic is added, an additive antihypertensive effect can be expected. In some cases this may necessitate a labetalol HCl dosage adjustment. As with most antihypertensive drugs, optimal dosages of NORMODYNE Tablets are usually lower in patients also receiving a diuretic.

When transferring patients from other antihypertensive drugs, NORMODYNE Tablets should be introduced as recommended and the dosage of the existing therapy progressively decreased.

### HOW SUPPLIED

NORMODYNE (labetalol HCl) Tablets, 100 mg, light-brown, round, scored, film-coated tablets engraved on one side with Schering and product identification numbers 244, and on the other side the number 100 for the strength and "NORMODYNE"; bottles of 100 (NDC-0085-0244-04), 500 (NDC-0085-0244-05), and box of 100 for unit-dose dispensing (NDC-0085-0244-08).

NORMODYNE (labetalol HCl) Tablets, 200 mg, white, round, scored, film-coated tablets engraved on one side with Schering and product identification numbers 752, and on the other side the number 200 for the strength and "NORMODYNE"; bottles of 100 (NDC-0085-0752-04), 500 (NDC-0085-0752-05), box of 100 for unit-dose dispensing (NDC-0085-0752-08), and Patient Calendar Package of 56 (4 bottles of 14 tablets) (NDC-0085-0752-03).

NORMODYNE (labetalol HCl) Tablets, 300 mg, blue, round, film-coated tablets engraved on one side with Schering and product identification numbers 438, and on the other side the number 300 for the strength and "NORMODYNE"; bottles of 100 (NDC-0085-0438-03), 500 (NDC-0085-0438-05), box of 100 for unit-dose dispensing (NDC-0085-0438-06), and Patient Calendar Package of 56 (4 bottles of 14 tablets) (NDC-0085-0438-02).

**NORMODYNE (labetalol HCl) Tablets should be stored between 2° and 30°C (36° and 86°F).**

**NORMODYNE (labetalol HCl) Tablets in the unit-dose boxes should be protected from excessive moisture.**

For complete prescribing information, please consult package insert.

Schering Corporation
Kenilworth, NJ 07033

Revised 3/85

Copyright © 1984, 1985, Schering Corporation. All rights reserved.

NR-542/13963800

(Continued from Page 782)

PHYSICIANS WANTED

## FAMILY PRACTICE RESIDENCY DIRECTOR

The White Memorial Medical Center of Los Angeles is seeking an ABFP certified Family Physician to further develop a new and exemplary Family Practice Residency. A strong candidate will possess excellent clinical, teaching, administrative and leadership skills and will be eligible for California licensure.

This developing residency anticipates accepting residents in 1988. It has the academic sponsorship of the Loma Linda Medical School and the academic support of the University of Southern California Medical School, through the Hispanic Medical Education and Training (HISMET) Program.

Salary and benefits are fully competitive. An appropriate academic appointment is available.

The White Memorial is an equal opportunity employer. Please send inquiries and résumés to:

**WMMC/HISMET Family Practice Residency Program**
**Department of Medical Education**
**White Memorial Medical Center**
**1720 Brooklyn Ave.**
**Los Angeles, CA 90033**

**MULTISPECIALTY GROUP** in San Francisco bay area looking for Board certified Family Practitioner for beautiful satellite office. Competitive salary and later incentive program. Contact David Louis, MD, 3100 Telegraph Ave, Oakland, CA 94609; (415) 273-8150.

**WE HAVE FULL- AND PART-TIME LOCUM TENENS** opportunities available with guaranteed incomes and paid malpractice. For more information, contact John Smith, Locum Tenens, Inc (A Division of Jackson and Coker), 400 Perimeter Center Terrace, Ste 760 WJM, Atlanta, GA 30346; Tel. 1 (800) 544-1987.

**CLAYPOOL.** Gila Medical Services Corporation seeks a Family Practice physician to provide medical care including OB and deliveries. Gila Medical Services operates a multispecialty group practice which provides routine primary medical care to the service area population of 29,000, with x-ray and lab services available on site. Salary and benefits commensurate with experience, with paid relocation expense. Claypool, Arizona is located almost equidistant from Phoenix and Tucson in Gila County. Reply to AHPR, 3131 E. Second St, Tucson, AZ 85716; (602) 626-7946.

## WASHINGTON STATE

The Wenatchee Valley Clinic, a multispecialty group of 105 physicians, has several practice opportunities throughout its seven practice locations. Currently we are seeking:

**MAIN FACILITY—WENATCHEE**

- **Pediatrics**
- **Allergy**
- **Nephrology**
- **Psychiatry**
- **General Internal Medicine**

**SATELLITE FACILITIES—OMAK/MOSES LAKE**

- **Orthopedics**
- **General Surgery**
- **General Internal Medicine**
- **OB/GYN**
- **Radiology**

All positions offer an excellent compensation and benefit package. North central Washington provides a high quality of life for those interested in an abundance of recreational opportunities in a family-oriented rural setting. If interested, send your CV to Dr Gerald Gibbons, Medical Director, Wenatchee Valley Clinic, 820 N. Chelan Ave, Wenatchee, WA 98801, or call (509) 663-8711, ext 205.

PHYSICIANS WANTED

## Western States OPENINGS

Many multispecialty groups and hospitals have asked us to recruit for over 300 positions of various specialties.

**Western States Physician Services**
**407 S. Clovis Ave, Ste 108**
**Fresno, CA 93727; (209) 252-3000**

**NORTHERN CALIFORNIA, EMERGENCY MEDICINE.** Full-time positions available in the Emergency Department at the University of California, Davis, Medical Center. The University serves a large region of northern California and is a major trauma center. Emergency physicians teach and supervise medical students and housestaff (240 per year) in addition to treating patients. Emergency Department physicians also provide medical control for UCDMC Life Flight, director of base station activities, and are actively involved in trauma care. Opportunities exist for involvement in other UCD School of Medicine teaching activities. Applicants should send CV to Robert W. Derlet, MD, Chief, Division of Emergency Medicine, University of California, Davis, Medical Center, 2315 Stockton Blvd, Sacramento, CA 95817.

**NEAR SAN FRANCISCO BAY AREA.** Board eligible Internist to join 4 other Internists in private practice covering rural ER/Acute Medicine. Involves four two-night shifts per month. Scheduling flexible. Sense of humor preferred. 60K per year. Charles Rath, MD, 199 E. Webster St, Colusa, CA 95932; (916) 458-7739.

**DIRECTOR OF NEW INTENSIVE CARE UNIT, MEDICAL-SURGICAL.** BC in major specialty, preferably Medicine, Surgery, or Anesthesiology is required with additional qualifications and experience desired. Prefer person who enjoys teaching and works well with nursing and medical staff. Minimum salary guarantee with time and opportunity for additional related practice. Kaweah Delta District Hospital is a 278-bed community hospital that is a major trauma and regional cancer center. Located in Visalia, California, a small business and agricultural community in the San Joaquin Valley of central California. Submit letter and recent CV to David L. Roberts, MD, Director of Medical Education, Kaweah Delta District Hospital, 400 W. Mineral King, Visalia, CA 93291; (209) 625-7308.

**PATHOLOGIST.** Associate needed for two-man group in southern California, 250-bed community hospital. Please send CV and pertinent references at first contact. $60,000-80,000 salary range depending on qualifications. Please contact Pathologist, PO Box 3249, Bakersfield, CA 93385.

**WYOMING.** Part-time position available in Lander, Wyoming for an ABEM certified/prepared Emergency Physician in low ED at Lander Valley Regional Medical Center. Have time to enjoy skiing, climbing, fishing, and camping in the Wind River Mountains, Tetons, and Yellowstone. Contact Wind River Emergency Physicians, PO Box 463, Lander, WY 82520.

**NEUROLOGIST.** An expanding HMO in San Francisco is seeking a BC Neurologist for a part-time position. Outpatient and inpatient responsibilities for consultations by referral. Send CV to Medical Director, PO Box 7883, San Francisco, CA 94120-9889.

*Ads Get Results!*

CLASSIFIED INFORMATION
**(415) 863-5522 EXTENSION 244**

PHYSICIANS WANTED

**SAN DIEGO, CALIFORNIA.** Career opportunities for full-time Family Practitioners and Internists with expanding network of ambulatory care centers. Send CV in confidence to Mercy CarePoint Medical Group, 681 Encinitas Blvd, Ste 406-W, Encinitas, CA 92024.

## SAN DIEGO

Growing, well-established multispecialty group in San Diego seeks well-trained Family Physician, Pediatrician, General Internist and Cardiologist to join in the group's expansion and enjoy a quality life-style. For further information and consideration, please forward CV to Miriam Stephens, Director/Professional Recruitment at: **SMITH HANNA MEDICAL GROUP, 5703 Oberlin Dr, #302-49, San Diego, CA 92121.**

**LAKE HAVASU CITY.** Immediate opportunity available for BE/BC Internist with subspecialty interest in Cardiology to establish private practice. Excellent practice potential for committed, active practitioner. Havasu Regional Hospital is willing to provide some start-up assistance. Lake Havasu City is located on the Colorado River where recreational activities abound. Reply to AHPR, 3131 E. Second St, Tucson, AZ 85716; (602) 626-7946.

**MINNEAPOLIS.** Seeks BC/BE associates in Adult Psychiatry, Cardiology, Family Practice, Internal Medicine, Obstetrics and Gynecology and Urology. Practice quality medicine in a prepaid multispecialty setting located in one of America's leading metropolitan areas. Comprehensive benefits, excellent facilities, flexible compensation programs. For further information about joining the Group Health medical staff, call Jerry Hess at (612) 623-8444 or write to Group Health, Inc, Attn: Jerry Hess, 2829 University Ave, SE, Minneapolis, MN 55414.

**FAMILY PRACTICE.** Excellent professional opportunity in beautiful north Idaho. Nominal lease at hospital owned clinic includes fully-equipped office, treatment suites and general receptionist. X-ray, lab and pharmacy on site. Located in 4-season playground rich with recreational opportunities. For information call Nancy at (208) 784-1221, ext 304, or send résumé to Shoshone Medical Center, Jacobs Gulch, Kellogg, ID 83837.

**BC OR BE ORTHOPEDIC SURGEON** wanted to join medical group in northern California. Beautiful facility, professional staff, offering an opportunity for both professional growth and stimulation with guaranteed salary, plus malpractice, health insurance, two weeks paid vacation the first year and a partnership percentage thereafter. Serious applicants please contact (916) 689-2040.

**PSYCHIATRIST.** Immediate position with Kern County Mental Health Department (Bakersfield, California). $57K to $73K. Requires California license (or eligibility) to practice medicine and 3 years residency in approved Psychiatry Program. Please contact Mr Ed Rous, Director, Kern County Mental Health Department, 1960 Flower St, Bakersfield, CA 93305; (805) 861-2251.

**GENERAL SURGEON.** Excellent opportunity for BC/BE in General Surgery. Close to San Francisco in beautiful wine country. Reply to Number 38, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

**EXCELLENT TEXAS OPPORTUNITIES.** General Surgeon, Internal Medicine, OB/GYN, Pediatrician, to practice in a community close to Houston. Enjoy country living at its best with the convenience of Houston within 40 minutes. New high-tech 150-bed hospital with good x-coverage, excellent quality of life. First year guarantee, etc. Reply with CV to Medical Support Services, Armando L. Frezza, 11509 Quarter Horse Trail, Austin, TX 78750; (512) 331-4164.

(Continued on Page 790)

(Continued from Page 789)

## PHYSICIANS WANTED

**CALIFORNIA FORENSIC MEDICAL GROUP, INC,** a corporation providing medical services in California county jails, has opportunities for physicians with a specialty in either Family Practice, General Practice or Internal Medicine. Send résumé to CFMG, Inc, PO Box 1831, Salinas, CA 93902; or contact Elaine Hustedt (408) 422-0214.

**CALIFORNIA, SAN FRANCISCO BAY AREA.** Full-time career Emergency Physician wanted for high-volume Emergency Department. Emergency Medicine Board certified or Board-ready mandatory to participate in a group of 20 full-time staff physicians seeing over 300 patients per day. Salaried position, excellent benefits include three weeks paid vacation; one week CME; paid malpractice, health and life insurance; corporate shareholdership in three years. Send CV or contact David Gallagher, MD, 27400 Hesperian Blvd, Hayward, CA 94545.

**ARIZONA-BASED PHYSICIAN** recruiting firm has opportunities coast-to-coast. "Quality Physicians for Quality Clients since 1972." Call (602) 990-8080; or send CV to Mitchell & Associates, Inc, PO Box 1804, Scottsdale, AZ 85252.

**FAMILY PHYSICIAN.** Residency trained, BC/BE. Currently a four-doctor group. Need to replace female partner who is leaving June 1987. OB optional. Current partners are also clinical faculty, UC Davis. Excellent community and hospital. Woodland is 15 miles from Sacramento and Davis. Contact J. T. Barrett, MD, W. J. Blevins Medical Center, 3 Court St, Woodland, CA 95695.

**FAMILY PRACTICE/INTERNAL MEDICINE/ENDOCRINOLOGY/CARDIOLOGY/OCCUPATIONAL MEDICINE** physicians, BC/BE needed immediately to join expanding multispecialty group. Practice in rapidly growing southwest community (population 500,000 plus). Fee-for-service and prepaid health care. Group includes Family Practice/Pediatrics/Internal Medicine/Subspecialties/24-hour Urgent Care. Teaching appointment. Position offers excellent compensation and benefits plus full pension and profit sharing. Relocation expenses. Interested individuals should reply with CV to Southwest Medical Associates, PO Box 15645, Las Vegas, NV 89114-5645.

**WYOMING—EMERGENCY MEDICINE.** Immediate opening. Full-time ER Physician. Pleasant working conditions. New hospital. Competitive compensation. Flexible scheduling. Paid malpractice. Small community life-style. Excellent outdoor recreation: camping, hunting, fishing, skiing and more. 72 miles to Salt Lake City. Send CV to Steven P. French, MD, Director, Emergency Department, 190 Arrowhead Dr, Evanston, WY 82930; (307) 789-3636.

**WORK PART-TIME.** Position available for Internist or GP/FP with Internal Medicine experience in Primary Care Practice, northern California Sierra foothills community of 25,000. Share rotating practice with two other MDs; you work one week in three. Outpatient and inpatient responsibilities (no OB, no ICU) in modern, fully-equipped 100-bed hospital. Minimum salary of $1,800/week (with incentives, actual will be around $2,200/week). Insurance, housing, and meals provided N/C. Send CV to David Lomba, 133 'B' Ascot Ct, Moraga, CA 94556.

**SACRAMENTO AREA.** Radiology. Interesting multioffice practice. Part-time and vacation coverage needed. Possible long-term association. Robert Swisher, MD, 729 Sunrise Ave—901, Roseville, CA 95661; (916) 786-9440.

**PHYSICIAN OPENING.** Ambulatory care/minor emergency center. Full- or part-time for FP/IM/EM trained/experienced physician. Located in Tacoma area. Flexible scheduling, pleasant setting, quality medicine. Contact David R. Kennel, MD, 5900-100th St SW, Ste 31, Tacoma, WA 98499; (206) 584-3023 or (206) 582-2542.

## PHYSICIANS WANTED

**PACIFIC NORTHWEST**
**Rapidly Growing, Low Risk Practice**
**Beautiful Country Setting**

Eight-person group seeks second OB/GYN to meet increased demand. 38-bed hospital equipped for mammography, ultrasound, and laparoscopy. Family-oriented community with easy access to Seattle and prime ski resort. Contact:

**The Friedrich Group, Inc.**
**9284 Ferncliff Northeast**
**Bainbridge Island, WA 98110**
**(206) 547-7850 or (206) 842-5248**

**THE IRVINE MEDICAL CENTER** and the University of California, Irvine, Department of Radiological Sciences are seeking a full-time faculty member for the Department of Radiological Sciences at the Clinical Assistant or Associate Professor level who would be assigned as Director of the Department of Radiology at Irvine Medical Center. The Irvine Medical Center is a new 177-bed hospital currently under construction in Irvine, California. Hospital opening is scheduled for fall of 1988. Administrative experience and academic background, including teaching and/or research, are required. Please send CV and the names of five references to Richard M. Friedenberg, MD, Professor and Chairman, Department of Radiological Sciences, University of California, Irvine, 101 City Dr South, Orange, CA 92668. The University of California is an affirmative action and an equal opportunity employer.

**CENTRAL WASHINGTON STATE.** Ambulatory care center seeks Primary Care Physician for full-time position. This challenging career opportunity offers a competitive salary/benefit package, interesting work, and adequate time off to enjoy the area's scenic beauty and abundant recreation. Contact Number 35, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

**CALIFORNIA, MERCED.** Emergency Department medical directorship and full-time staff opportunities are available at our client hospital in Merced. Full-service community hospital with moderate volume ED. Guaranteed rate of compensation, occurrence malpractice insurance coverage, CME allowance, reimbursement of professional dues, relocation allowance. Must be willing to live in community. For additional details contact Bill Salmo, Spectrum Emergency Care, 6275 Lehman Dr, Ste C-202, Colorado Springs, CO 80918; 1 (800) 525-3681; (303) 590-1755.

**MEDICAL OFFICER (OCCUPATIONAL MEDICINE).** GM-602-13, salary range $47,911 to $59,268; Naval Medical Clinic, Occupational Medical Branch, Port Hueneme, California; send résumés to NCBC, Code 231 (M. Presley), Bldg 14, Rm 157, Port Hueneme, CA 93043-5000; or call (805) 982-4473.

**CASA GRANDE.** Family Health Center in community with new 100-bed hospital, located between Phoenix and Tucson needs dynamic Family Practice physician (BC/BE) willing to do OB and deliveries. Guaranteed first year salary, bonus and paid malpractice insurance, four weeks paid vacation. Send CV to AHPR, 3131 E. Second St, Tucson, AZ 85716; (602) 626-7946.

**INTERNAL MEDICINE.** San Francisco suburb. BC/BE associate needed for busy solo practice adjacent to Mount Diablo Hospital. Send CV to Number 41, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

**INTERNIST** position available with 35 member multispecialty group; BC/BE; immediate opening; full range of benefits plus immediate shareholder status; excellent opportunity; central coast of California. Respond with CV to Colin J. Wells, MD, San Luis Medical Clinic, Ltd, 1235 Osos St, San Luis Obispo, CA 93401-3619. NO PHONE CALLS PLEASE.

## PHYSICIANS WANTED

**PSYCHIATRIC RESIDENT.** Specific duties involve taking medical and psychiatric histories, performing physical examinations, establishing diagnoses, and designing and implementing treatment plans as a psychiatric resident. Job entails the clinical practice of medicine in a university teaching institution under careful supervision. MD degree required. Position is full-time with additional evening and weekend on call responsibilities. Salary: $17,650 per annum. Apply by résumé (Reference Job Order #328764) to Job Services, PO Box 829, Fargo, ND 58107.

**MONTANA.** Emergency Physician needed in expanding ER group in the beautiful Bitterroot Valley of western Montana. Contact Jim Hansen, MD, PO Box 1262, Hamilton, MT 59840; (406) 363-2526.

## SITUATION WANTED

**INTERNIST.** Board certified in Internal Medicine, desires full-time employment with group or HMO. Physician also has subspecialty of Oncology and Hematology. Will practice primary care Internal Medicine and/or Oncology and Hematology. Also interested in position of medical or hospital administrator. Physician has private practice and HMO experience. Site must be within 45 minutes or 25 miles of Long Beach, California. Available May 1987. Please call David Dworkin, MD, at (213) 494-7473 or (714) 722-6926 or write to 6250 Majorca Cir, Long Beach, CA 90803.

**EXPERIENCED NEUROLOGIST, BC,** with 4 years' experience performing and interpreting MRI and CT of head and spine as well as carotid ultrasound. Seeks affiliation with group needing expertise in these areas. Reply to Number 39, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

## LOCUM TENENS

**LOCUM TENENS PATHOLOGIST AVAILABLE.** Board certified AP/CP, experienced. Previous clinical experience. US graduate. Prefer 1 month or longer. References upon request. Reply to Number 40, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

**LOCUM TENENS, INC.** (A Division of Jackson and Coker), can staff your practice from 2 weeks to 52 weeks, malpractice insurance for all 50 states, contact John Smith, 400 Perimeter Center Terrace, Suite 760 WJM, Atlanta, GA 30346; Tel. 1 (800) 544-1987.

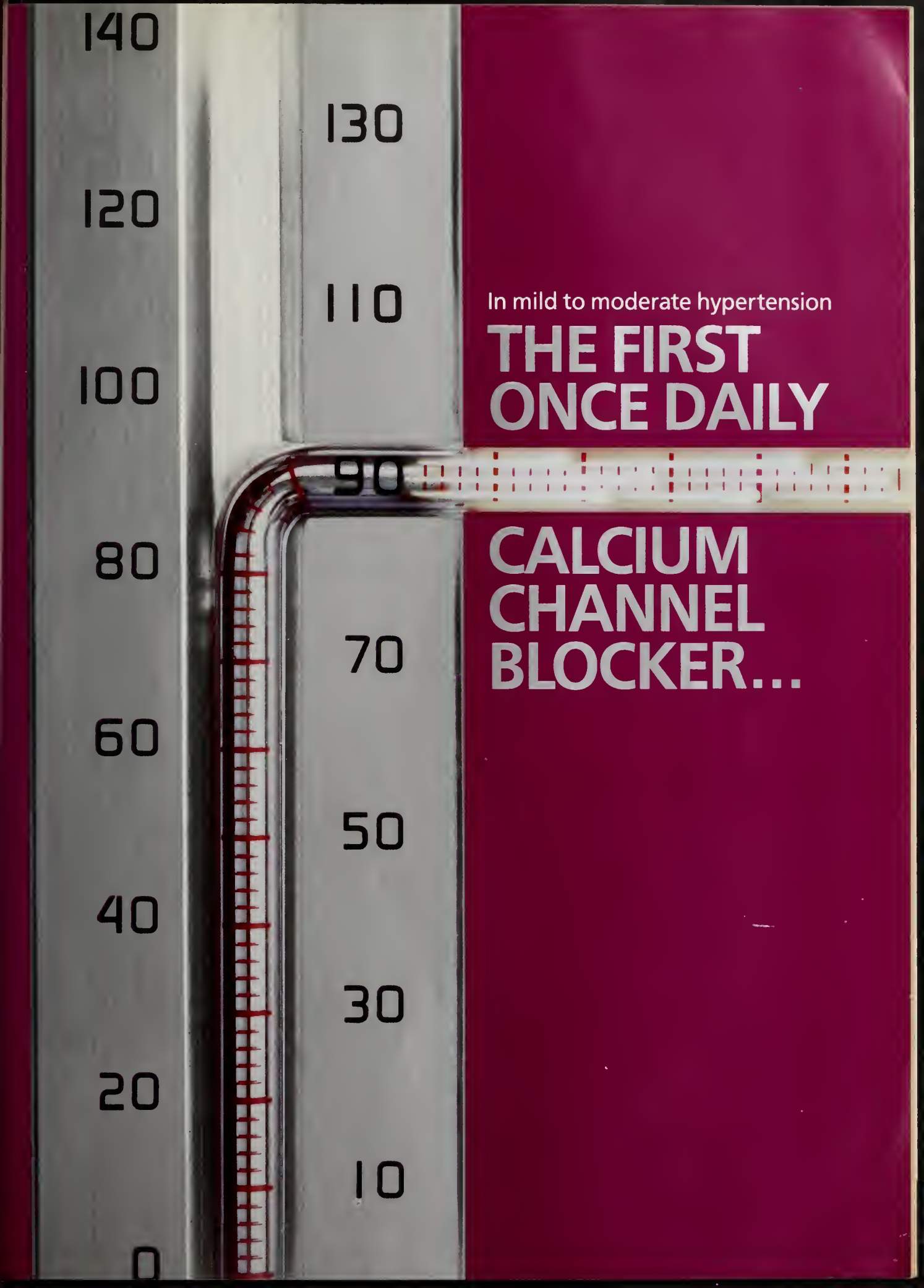
**LOCUM TENENS SERVICE**
**WESTERN PHYSICIANS REGISTRY**

*. . . offers coverage for vacation or continuing education. To arrange coverage for your practice or to participate as temporary physician, contact:* **Carol Sweig, Director, 1315 Evans Ave, San Francisco, CA 94124; (415) 826-7676.**

Ads Get Results!

CLASSIFIED INFORMATION
**(415) 863-5522 EXTENSION 244**

(Continued on Page 792)


140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
In mild to moderate hypertension
THE FIRST ONCE DAILY
CALCIUM CHANNEL BLOCKER...

**NEW**
ONCE DAILY

# ISOPTIN SR*

## (verapamil HCl/Knoll)

*240 mg scored, sustained-release tablets*

**JAMES B.**
38, black male, heavy smoker. Prescribed a diuretic by another physician last year for hypertension.

**YOUR CONCERNS**
Presents with "smoker's cough." Workup reveals a BP of 150/107.

**A LOGICAL CHOICE FOR CONTROL OF HIS BP**
ISOPTIN* (verapamil HCl/Knoll) because...
— Black hypertensives often have low plasma renin activity and generally do not respond favorably to beta blockers.
— Beta blockers may increase the likelihood of bronchospasm.

**ALICE W.**
65, diabetic, overweight. Her BP has elevated to 190/98.

**YOUR CONCERNS**
She's on daily insulin.

**A LOGICAL CHOICE FOR CONTROL OF HER BP**
ISOPTIN* (verapamil HCl/Knoll) because...
— Unlike most beta blockers and diuretics, ISOPTIN has no adverse effects on serum glucose levels.
— Unlike most beta blockers, ISOPTIN does not mask the symptoms of hypoglycemia.

**THOMAS G.**
70, asthmatic. In the past, BP adequately controlled with 25 mg hydrochlorothiazide daily.

**YOUR CONCERNS**
Today patient presents with symptoms of gout. Workup reveals high uric acid level, low serum potassium, and BP elevated to 180/98.

**A LOGICAL CHOICE FOR CONTROL OF HIS BP**
ISOPTIN* (verapamil HCl/Knoll) because...
— Unlike diuretics, ISOPTIN will not decrease serum potassium levels or elevate uric acid levels.
— Unlike beta blockers, ISOPTIN can be used safely in asthma and COPD patients.

**JOHN K.**
42, Annual physical uncovered diastolic BP of 102... confirmed on three successive office visits. Unresponsive to nonpharmacologic intervention.

**YOUR CONCERNS**
Salesman, spends many hours of his working day in car... total cholesterol level 300, HDL 35.

**A LOGICAL CHOICE FOR CONTROL OF HIS BP**
ISOPTIN* (verapamil HCl/Knoll) because...
— Unlike diuretics, ISOPTIN does not cause urinary urgency.
— Unlike either beta blockers or diuretics, ISOPTIN will not adversely affect his already seriously compromised lipid profile.
— Unlike with propranolol, fatigue and impotence are rarely reported.

## *Antihypertensive therapy you and your patients can live with*

*A product of Knoll research.

© 1986, BASF K & F Corporation

2538/2-87

Knoll Pharmaceuticals
A Unit of BASF K&F Corporation
Whippany, New Jersey 07981

BASF Group

knoll®

Printed in U.S.A.

Please see adjacent page for brief summary.

*In mild to moderate hypertension*

Brief Summary

***THE FIRST ONCE DAILY CALCIUM CHANNEL BLOCKER***

## ISOPTIN® SR (verapamil HCl/Knoll) 240 mg scored, sustained-release tablets

**CONTRAINDICATIONS:** 1) Severe left ventricular dysfunction (see WARNINGS), 2) Hypotension (less than 90 mmHg systolic pressure) or cardiogenic shock, 3) Sick sinus syndrome or 2nd or 3rd degree AV block (except in patients with a functioning artificial ventricular pacemaker).

**WARNINGS: Heart Failure:** ISOPTIN should be avoided in patients with severe left ventricular dysfunction (see DRUG INTERACTIONS). Patients with milder ventricular dysfunction should, if possible, be controlled before verapamil treatment. Hypotension: ISOPTIN (verapamil HCl) may produce occasional symptomatic hypotension. Elevated Liver Enzymes: Elevations of transaminases with and without concomitant elevations in alkaline phosphatase and bilirubin have been reported. Periodic monitoring of liver function in patients receiving verapamil is therefore prudent. Accessory Bypass Tract (Wolff-Parkinson-White): Patients with paroxysmal and/or chronic atrial flutter or atrial fibrillation and a coexisting accessory AV pathway have developed increased antegrade conduction across the accessory pathway producing a very rapid ventricular response or ventricular fibrillation after receiving intravenous verapamil. While this has not been reported with oral verapamil, it should be considered a potential risk. Treatment is usually D.C.-cardioversion. Atrioventricular Block: The effect of verapamil on AV conduction and the SA node may cause asymptomatic 1st degree AV block and transient bradycardia. Higher degrees of AV block, while infrequent (0.8%), may require a reduction in dosage or, in rare instances, discontinuation of verapamil HCl. Patients with Hypertrophic Cardiomyopathy (IHSS): Although verapamil has been used in the therapy of patients with IHSS, severe cardiovascular decompensation and death have been noted in this patient population.

**PRECAUTIONS: Impaired Hepatic or Renal Function:** Verapamil is highly metabolized by the liver with about 70% of an administered dose excreted in the urine. In patients with impaired hepatic or renal function verapamil should be administered cautiously and the patients monitored for abnormal prolongation of the PR interval or other signs of excessive pharmacological effects (see OVERDOSAGE).

**Drug Interactions:** Beta Blockers: Concomitant use of ISOPTIN and oral beta-adrenergic blocking agents may be beneficial in certain patients with chronic stable angina or hypertension, but available information is not sufficient to predict with confidence the effects of concurrent treatment in patients with left ventricular dysfunction or cardiac conduction abnormalities. Digitalis: Clinical use of verapamil in digitalized patients has shown the combination to be well tolerated if digoxin doses are properly adjusted. However, chronic verapamil treatment increases serum digoxin levels by 50 to 75% during the first week of therapy and this can result in digitalis toxicity. Upon discontinuation of ISOPTIN (verapamil HCl), the patient should be reassessed to avoid underdigitalization. Antihypertensive Agents: Verapamil administered concomitantly with oral antihypertensive agents (e.g., vasodilators, angiotensin-converting enzyme inhibitors, diuretics, beta blockers, prazosin) will usually have an additive effect on lowering blood pressure. Patients receiving these combinations should be appropriately monitored. Disopyramide: Disopyramide should not be administered within 48 hours before or 24 hours after verapamil administration. Quinidine: In patients with hypertrophic cardiomyopathy (IHSS), concomitant use of verapamil and quinidine resulted in significant hypotension. There has been a report of increased quinidine levels during verapamil therapy. Nitrates: The pharmacologic profile of verapamil and nitrates as well as clinical experience suggest beneficial interactions. Cimetidine: Two clinical trials have shown a lack of significant verapamil interaction with cimetidine. A third study showed cimetidine reduced verapamil clearance and increased elimination to 1/2. Anesthetic Agents: Verapamil may potentiate the activity of neuromuscular blocking agents and inhalation anesthetics. Carbamazepine: Verapamil may increase carbamazepine concentrations during combined therapy. Rifampin: Therapy with rifampin may markedly reduce oral verapamil bioavailability. Lithium: Verapamil may lower lithium levels in patient on chronic oral lithium therapy. Carcinogenesis, Mutagenesis, Impairment of Fertility: There was no evidence of a carcinogenic potential of verapamil administered to rats for two years. Verapamil was not mutagenic in the Ames test. Studies in female rats did not show impaired fertility. Effects on male fertility have not been determined. Pregnancy (Category C): There are no adequate and well-controlled studies in pregnant women. ISOPTIN crosses the placental barrier and can be detected in umbilical vein blood at delivery. This drug should be used during pregnancy, labor, and delivery, only if clearly needed. Nursing Mothers: ISOPTIN is excreted in human milk, therefore, nursing should be discontinued while verapamil is administered. Pediatric Use: Safety and efficacy of ISOPTIN in children below the age of 18 years have not been established.

**ADVERSE REACTIONS:** Constipation 8.4%, dizziness 3.5%, nausea 2.7%, hypotension 2.5%, edema 2.1%, headache 1.9%, CHF/pulmonary edema 1.8%, fatigue 1.7%, bradycardia 1.4%, 3° AV block 0.8%, flushing 0.1%, elevated liver enzymes (see WARNINGS). The following reactions, reported in less than 1.0% of patients, occurred under conditions (open trials, marketing experience) where a causal relationship is uncertain; they are mentioned to alert the physician to a possible relationship: angina pectoris, arthralgia and rash, AV block, blurred vision, cerebrovascular accident, chest pain, claudication, confusion, diarrhea, dry mouth, dyspnea, ecchymosis or bruising, equilibrium disorders, exanthema, gastrointestinal distress, gingival hyperplasia, gynecomastia, hair loss, hyperkeratosis, impotence, increased urination, insomnia, macules, muscle cramps, myocardial infarction, palpitations, paresthesia, psychotic symptoms, purpura (vasculitis), shakiness, somnolence, spotty menstruation, sweating, syncope, urticaria. Treatment of Acute Cardiovascular Adverse Reactions: Whenever severe hypotension or complete AV block occur following oral administration of verapamil, the appropriate emergency measures should be applied immediately, e.g., intravenously administered isoproterenol HCl, levarterenol bitartrate, atropine (all in the usual doses), or calcium gluconate (10% solution). If further support is necessary, inotropic agents (dopamine or dobutamine) may be administered. Actual treatment and dosage should depend on the severity and the clinical situation and the judgment and experience of the treating physician.

**OVERDOSAGE:** Treatment of overdosage should be supportive. Beta-adrenergic stimulation or parenteral administration of calcium solutions may increase calcium ion flux across the slow channel, and have been used effectively in treatment of deliberate overdosage with verapamil. Clinically significant hypotensive reactions or fixed high degree AV block should be treated with vasopressor agents or cardiac pacing, respectively. Asystole should be handled by the usual measures including cardiopulmonary resuscitation.

**Knoll Pharmaceuticals**
A Unit of BASF K&F Corporation
Whippany, New Jersey 07981

knoll®

**BASF** Group

©1986, BASF K&F Corporation 2474/11/86 Printed in U.S.A.

# PART-TIME MEDICAL CONSULTANT CONTRACTS

Physicians needed to work under contract, on a part-time basis for the Social Security Administration's Disability Insurance Program. Involves review of medical evidence in disability claims at 100 Van Ness Avenue, San Francisco, California. No patient contact. Applicants must: (1) have a valid license to practice medicine in the USA; (2) have recent or current clinical experience; and (3) be available between 7:00 a.m. and 4:30 p.m., Monday through Friday for case review. Subject to change, the specialties needed are Cardiology, Pulmonary Medicine, Psychiatry and Neurology. In addition to physicians for medical review, a chief medical consultant (Regional Medical Advisor) is needed. This is an administrative position and, in addition to the above criteria, one year's experience in the Disability Programs Branch is required. Applicants for this position should be available approximately 20 hours per week. Women and minorities are encouraged to apply. If interested in applying please submit a current curriculum vitae by July 15, 1987 to the address shown below. The curriculum vitae should address the following selection factors:

## Selection Criteria

1. **Medical Training**

   Identity specialty, training facility, dates, and number of years in specialty. Please indicate if you are Board eligible or certified and in what specialty.

2. **Medical Experience** (Current and Past)

   A. Clinical Practice

   Identify dates, location and nature of clinical practice and experience and whether full time or part time.

   B. Other Experience

   Identify other professional activities and experience such as teaching, publications, involvement with committees and professional organizations, etc.

3. **Disability Claims Experience,** reviewing evidence of record in order to evaluate claims for benefits:

   A. Type of claims

   B. Agency

   C. From To

   D. Approximate number of claims reviewed.

4. **Availability** (Between the hours of 7:00 a.m.-4:30 p.m.)

   Approximate hours and days available for case review:

   MON ____ TUE ____ WED ____ THU ____ FRI ____

   When addressing availability, please indicate the maximum in terms of *both* days and hours that you would be available if requested by the Social Security Administration.

In addition to the above criteria, the following will be considered for the position of Regional Medical Advisor:

5. **Administrative/Management/Leadership Experience**

   A. Experience providing direction to other physicians in medical and program areas.

   B. Experience providing medical guidance to non-medical personnel in the formulation of policy and procedures.

   C. Experience in developing governmental regulations.

   D. Demonstrated leadership in professional organizations.

6. **Training of Physicians**

   A. Experience in training physicians in governmental regulations, policies, and procedures.

   B. Other relevant educational/training experience.

Your curriculum vitae and the above information should be sent to:

Contracting Officer
Department of Health and Human Services
50 United Nations Plaza, Room 403
San Francisco, CA 94102

(Continued from Page 790)

## PRACTICES AVAILABLE

**FAMILY PRACTICE-GENERAL SURGERY.** Multiple practice situation, long established. Prime Orange County, California beach city location. Adjacent to modern hospital with ICU/CCU. Includes equipment, assumable lease. Reply to Number 17, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

**FOR SALE ESTABLISHED NEUROLOGY PRACTICE.** 40 miles south of Seattle next to major adult and ped. hospital. CT, MRI available; share call. EEG, EMG, evoked potentials in office. Gross $280K, sell $60K plus acct. rec. (if desired), financing available. Available 1987, retire for health reasons and available during transition. Call (206) 572-8663, leave name and phone. Will return call after hours.

**ACTIVE ADULT AND PEDIATRIC ALLERGY PRACTICE** for sale in Albuquerque, New Mexico. Available immediately. Pleasant climate—good gross—excellent hours—and negotiable terms. Reply Number 33, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

**PHOENIX FAMILY PRACTICE.** Solo adult practice, excellent location, collections over $250,000. Write or call Mr Rinde, PO Box 444436, Phoenix, AZ 86064; (602) 224-0349.

**INTERNAL MEDICINE PRACTICE FOR SALE.** Aptos, California "On the Monterey Bay." 39 year established, responsible private practice. Three excellent hospitals within 10 mile radius. All specialties available. Limited to Board eligible or certified Internists. Contact: Administrator, PO Box 325, Aptos, CA 95001; (408) 688-3071.

**GP/FP PRACTICE IN MID-ORANGE COUNTY.** Established over 35 years. Collects almost $300K yearly with a very high net of $190K. Unusually well equipped. Buyer must provide financing for purchase of the practice and A.R. ($100K plus). No Medi-Cal. Wonderful opportunity. Call S. Mendlowitz, Attorney, (213) 420-1351.

**FOR SALE.** San Francisco, California Family Practice, OB optional. (415) 221-0325.

**FOR SALE.** Well-established internal medical practice; 2 offices–Los Angeles and Beverly Hills. Gross $3,000,000 plus. $100,000 down and an additional $25,000 per year for four years. Qualified buyers only. Please reply to Number 37, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

## PRACTICE OPPORTUNITIES

**CALIFORNIA/NATIONWIDE.** Derm, IM, Ophthal, OB/GYN, Otolaryngology, Neurosurgery, Occupational, FP, ENT, Urology, Hematology/Oncology, Surg, Allergy, Ortho, Psych, Pulm, Radiology, Rheum, Ped plus many others. Mary Bradshaw, Practice Sales/Recruiter, Valuations, 21 Altamount Dr, Orinda, CA 94563; (415) 376-0762.

## COMPUTER INFORMATION

**COMPUTERIZE YOUR MEDICAL BILLING.** Remarkably easy-to-use software. Prints bills, statements, insurance forms. Menu-driven. Reports aging balances, referral sources, income by time period, medical procedure codes and more. Installs automatically. IBM and compatibles-hard disk or floppies. Solo practice only $399. Group practice only $499 (Calif add tax) MC/Visa. Full customer support. Demo disk w/46-pg manual ($10 + $3 s/h). Call or write REM Systems, Inc, 180 Emerson St, Palo Alto, CA 94301; (415) 322-0369.

Ads Get Results!
CLASSIFIED INFORMATION
(415) 863-5522 EXTENSION 244

## MISCELLANEOUS

**VACATION HOME.** Escape to the southern Gulf Islands of British Columbia, Canada. Rent a new ocean front home with spectacular views and all amenities. Enjoy the pool, spa, sauna, king size beds and gourmet kitchen. Walk in the peaceful natural setting, or take in the many island activities. Ideal for one or two couples. For more information and reservations write Escape, 25340 76th Ave, Aldergrove, BC, VOX 1AO Canada.

*MEDICAL SPANISH — EASY!*
Speak to patients in everyday Spanish.
*Complete 6-cassette course with manual/dictionary, pocket guide. All basic terms and procedures: $95 plus tax.
RESULTS GUARANTEED OR MONEY REFUNDED!
CALL/WRITE FOR FACTS ON OTHER MATERIALS, FREE
MEDICAL SPANISH NEWSLETTER!
CSLA
CALIFORNIA SPANISH LANGUAGE ASSOC.
P.O. Box 3522-J, San Diego, CA 92073-0590
(619) 544-0548

## MEDICAL EQUIPMENT

**50% OFF PREVIOUSLY OWNED MEDICAL** laboratory, x-ray, ultrasound equipment. We buy, sell, broker, repair. APPRAISALS AVAILABLE by Certified Surgical Consultant. Medical Equipment Resale and Repair, Inc, 24026 Haggerty Rd, Farmington Hills, MI 48018. 1 (800) 247-5826, (313) 477-6880.

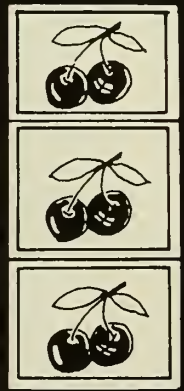
## SEMINARS

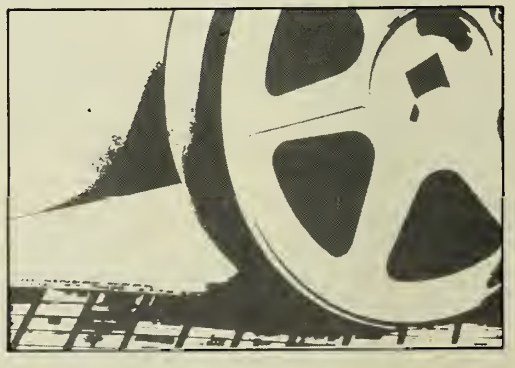
**MALPRACTICE AND PRACTICE MANAGEMENT TAX DEDUCTIBLE SEMINARS** held weekly in San Francisco, Lake Tahoe, San Diego, and Anaheim. Call California Seminars at 1 (800) 325-7934. In California call 1 (800) 526-6699.

**ADVANCED CARDIAC LIFE SUPPORT IN LAKE TAHOE**
**PROVIDER AND RECERTIFICATION**
September 11, 12, and 13, 1987. AHA certified.
Cal Neva Lodge at Incline Village
Group lodging rates available
**CPR Seminars, 833 Market St, Ste 421**
**San Francisco, CA 94103; (415) 543-7282**

**BOARD REVIEW IN CRITICAL CARE MEDICINE (ACLS Option)**
October 7-11, 1987—Portland, Oregon
School of Medicine
Oregon Health Sciences University
**CME-GH, OHSU, Portland, OR 97201**
**(503) 225-8700**

Ads Get Results!
CLASSIFIED INFORMATION
(415) 863-5522 EXTENSION 244

ADS GET RESULTS

CLASSIFIED INFO
(415) 863-5522
EXT 244

This Publication is available in Microform.

University Microfilms International
Please send additional information
for _____ (name of publication)
Name_____
Institution_____
Street_____
City_____
State_____ Zip_____
300 North Zeeb Road, Dept. P.R., Ann Arbor, MI 48106

# WYOMING MEDICAL SOCIETY

84th ANNUAL MEETING WMS HOUSE OF DELEGATES AND SCIENTIFIC SESSION

JUNE 25-28, 1987 • JACKSON LAKE LODGE, MORAN, WYOMING • GRAND TETON NATIONAL PARK

## WMS ANNUAL MEETING AND SCIENTIFIC SESSION

### THE LABORATORY'S CONTRIBUTION TO CLINICAL MEDICINE

### THURSDAY, JUNE 25, 1987

8:00 AM REGISTRATION/EXHIBITS

8:30 AM WMS HOUSE OF DELEGATES OPENING SESSION

10:30 AM REFERENCE COMMITTEES

1:15 PM LEE K. HERMANN, MD
WMS President
*Welcoming Remarks*

1:30 PM CARL E. SPEICHER, MD
*The Laboratory and the Healthy Patient: What Do We Really Need?*

2:15 PM CARL E. SPEICHER, MD
*The Outpatient: A Look at the More Common Diagnostic Problems, New Aspects of Laboratory Testing*

3:00 PM Coffee Break

3:15 PM JOHN C. NEFF, MD
*Infectious Mononucleosis: The Child, the Adolescent and the Adult—Current Concepts*

4:00 PM QUESTION AND ANSWER ROUNDTABLE

4:30 PM RECESS SCIENTIFIC SESSION

6:00 PM WELCOME TO THE TETONS SOCIAL HOUR
(Hosted by The Doctors' Company)

### FRIDAY, JUNE 26, 1987

8:00 AM REGISTRATION/EXHIBITS

9:00 AM LEE K. HERMANN, MD
*Introductory Remarks*

9:00 AM ARTHUR E. PELLEGRINI, MD
*What Is That Funny Looking Pigmented Skin Lesion?*

9:45 AM ARTHUR E. PELLEGRINI, MD
*Current Therapeutic Approaches to the Aggressive Melanocytic Tumors*

10:30 AM Coffee Break

10:45 AM CARL E. SPEICHER, MD
*Problem Cases Within the Hospital: The Contribution of the Laboratory*

11:30 AM QUESTION AND ANSWER ROUNDTABLE

11:45 AM Lunch Break

2:00 PM THE DOCTORS' COMPANY RISK MANAGEMENT TEAM
*A Mock Trial*

4:00 PM Recess Scientific Session

6:00 PM WMS PRESIDENT'S RECEPTION AND BANQUET
MICHAEL J. SULLIVAN
Governor of Wyoming, *Speaker*
*Entertainment and Dancing*

### SATURDAY, JUNE 27, 1987

8:00 AM REGISTRATION/EXHIBITS

9:00 AM LEE K. HERMANN, MD
*Introductory Remarks*

9:00 AM JOHN C. NEFF, MD
*Hepatitis: Current Applications of the Serologic Markers*

9:45 AM JAMES M. AVENT, MD
*The Thin Needle: Uses and Abuses*

10:30 AM Coffee Break

10:45 AM JOHN C. NEFF, MD
*Let's Look at the Complications of Blood Transfusions*

11:30 AM QUESTION AND ANSWER ROUNDTABLE

12 NOON Recess Scientific Session
*Afternoon Free*

6:00 PM SOCIAL HOUR
(Hosted by Capitol Recoveries)

### SUNDAY, JUNE 28, 1987

9:00 AM WMS HOUSE OF DELEGATES CLOSING SESSION

### FACULTY

**James M. Avent, MD**
Assistant Professor
University of Utah
Cytopathologist
St. Mark's Hospital
Salt Lake City

**John C. Neff, MD**
Professor of Pathology
Ohio State University
Columbus, Ohio

**Arthur Pellegrini, MD**
Captain, United States Navy
Department of Dermatology
United States Naval Hospital
San Diego

**Carl E. Speicher, MD**
Professor of Pathology
Director of Clinical Labs
Ohio State University
Columbus, Ohio

**Risk Management Team**
The Doctors' Company
Santa Monica, California

WYOMING Medical Society

WYOMING MEDICAL SOCIETY
P.O. Box 4009
Cheyenne, WY 82003-4009
Phone (307) 635-2424

**REGISTRATION FORM FOR PHYSICIANS ATTENDING THE WMS ANNUAL MEETING**

JUNE 25-28,1987 • JACKSON LAKE LODGE • MORAN, WYOMING

NAME _____ SPOUSE'S NAME _____

ADDRESS _____ ZIP _____

____ Registration Fee ($80 for members $100 for nonmembers) . . . . . $_____

____ Banquet tickets @ $25 per person . . . . . $_____

____ Auxiliary Luncheon tickets @ $10 per person . . . . . $_____

TOTAL $_____

Checks made payable to the Wyoming Medical Society must accompany this form and be sent to:

WYOMING MEDICAL SOCIETY
P.O. DRAWER 4009
CHEYENNE, WY 82003

____ Send Jackson Lake Lodge reservation form and Grand Teton Park lodging information.

# The complete journal for family practice physicians

- Reaches 79,000 family physicians monthly
- Presents the most commonly seen patient problems in family practice
- Written by physicians for physicians
- The most current clinical updates in:

| | |
|---|---|
| Cardiology | Ob/Gyn |
| Diabetes | Psychiatry |
| Pediatrics | Gastroenterology |

- Provides 20 hours of CME Category 1 Credit

**PRACTICAL • CLINICAL • EDUCATIONAL • CURRENT**


## CONTINUING MEDICAL EDUCATION

*(Continued from Page 784)*

### PEDIATRICS

July 24-25—**Debates and Updates in Pediatric Emergencies.** UCSF at Hyatt on Union Square, San Francisco. Fri-Sat. 14 hrs. $235. Contact: UCSF.

September 12-13—**44th Annual Brennemann Memorial Lectures.** Los Angeles Pediatric Society at Sheraton Universal Hotel, Los Angeles. Sat-Sun. Contact: Los Angeles Pediatric Society, PO Box 9022, Inglewood 90305. (213) 757-1198.

October 10-17—**11th Annual Pediatrics for the Practitioner.** UCI at Mauna Kea Beach, Hawaii. One week. Contact: UCI.

October 16-17—**2nd Annual Symposium on Advanced Pediatric Emergency Medicine and Trauma.** UCI at Long Beach Airport Marriott Hotel. Fri-Sat. Contact: UCI.

October 16-18—**Current Advances in Pediatrics.** American Academy of Pediatrics and UCI at Disneyland Hotel, Anaheim. Fri-Sun. Contact: AAP, PO Box 1297, Orange 92668. (714) 978-2415.

October 23-25—**Current Concepts in Pediatric Gastroenterology.** Children's Hospital, Oakland at Doubletree Hotel, Monerey. Fri-Sun. Contact: Kim Leadon, CME Office, Children's Hospital, 747 52nd St, Oakland 94609. (415) 428-3021.

November 20-23—**9th Annual Las Vegas Seminars—Pediatric Update.** Los Angeles Pediatric Society at Caesar's Palace. Fri-Mon. Contact: Eve Black, Los Angeles Pediatric Society, PO Box 2022, Inglewood 90305. (213) 757-1198.

### PSYCHIATRY

October 17-18—**Dynamics of Human Development—Implications for Treatment.** Continuing Education Seminars at Los Angeles. Sat-Sun. 11.5 hrs. $175. Contact: Continuing Education Seminars, 1023 Westholme Ave, Los Angeles 90024. (213) 475-8300.

November 6-8—**33rd Annual: Group Therapy Symposium.** UCSF at Cathedral Hill Hotel, San Francisco. Fri-Sun. Contact: UCSF.

### RADIOLOGY

July 11-12—**Two-Day Seminar in Breast Imaging With Interpretive Workshops.** Los Angeles Radiological Society at Century Plaza Hotel, Los Angeles. Sat-Sun. 10 hrs. $25-200. Contact: LARS, PO Box 91215, Los Angeles 90009-1215. (213) 642-0921.

August 3-7—**Diagnostic Radiology Seminars.** UCSF at Hyatt Regency, Maui, Hawaii. Mon-Fri. 27.5 hrs. $495. Contact: UCSF.

August 3-7—**Modern Radiology Practice.** UCSD at Red Lion Ocean Resort, Santa Barbara. Mon-Fri. 30 hrs. $250-425. Contact: Dawne Ryals, PO Box 920113, Norcross, GA 30092-0113. (404) 641-9773.

August 8-9—**Magnetic Resonance Imaging Update and New Techniques: A Mini-Symposium.** Hoag Memorial Presbyterian Hospital at Ritz-Carlton Hotel, Laguna Niguel. Sat-Sun. 12 hrs. $175. Contact: Dawne Ryals, PO Box 920113. (404) 641-9773.

August 13-15—**Advanced Ultrasound.** American College of Obstetricians and Gynecologists at Silverado Inn, Napa. Thurs-Sat. Contact: Robin Murray, ACOG, 600 Maryland Ave SW, Washington, DC 20024-2588. (202) 638-5577.

August 22-29—**Radiology.** USC at Maui Marriott Hotel, Maui, Hawaii. One week. 26 hrs. $525. Contact: USC.

August 26-28—**Interventional Radiology.** UCSF at Hyatt Regency Hotel, San Francisco. Wed-Fri. Contact: UCSF.

August 27-30—**3rd Annual Physics and Biology of Radiology.** UCSD at San Diego Town and Country Hotel. Thurs-Sun. 26.5 hrs. $395. Contact: Dawne Ryals, PO Box 920113, Norcross, GA 30092-0113. (404) 641-9773.

*(Continued on Page 797)*

# Your prescription now...

# for a lifetime of happy dental visits

**During the first months of life,** Vi-Flor® vitamin-fluoride supplements begin to enhance tooth morphology,[1] increase enamel hardness, and promote mineralization of unerupted teeth[2]—all while providing recommended minimum daily amounts of selected vitamins.

**Fluoride supplementation is both prophylactic *and* therapeutic,** especially with newborns who are already in the process of developing 20 primary and 32 permanent teeth. In fact, receiving adequate systemic fluoride beginning the first months of life can help reduce childhood cavities by 50-80%.[3]

And that *daily* use through age 16 results in optimal levels of fluoride supplementation, for a lifetime of stronger teeth and lower-cost dental care.

**Prescribe**
Vi-Flor® vitamin-fluoride supplements... now.
The essential first step begins with you, and...

**TRI·VI·FLOR®**
**POLY·VI·FLOR®**


**References:**

1. Moss SJ: The worldwide decline in caries prevention, in Mead Johnson Clinical Report Series, Clinical Importance of Fluoride Nutrition in Infants, Children, and Young Adults. Chicago, Pragmaton® 1985, Number 1, p. 2.

2. Newbrun E: How fluoride works: Topical vs. systemic action, in Mead Johnson Clinical Report Series, Clinical Importance of Fluoride Nutrition in Infants, Children, and Young Adults. Chicago, Pragmaton® 1985, Number 1, p. 5.

3. Aasenden R and Peebles T: Effects of fluoride supplementation from birth on human deciduous and permanent teeth. *Arch Oral Biol* 1974;19:321.


Mead Johnson
NUTRITIONAL DIVISION


© 1987 Bristol-Myers U.S. Pharmaceutical and Nutritional Group • Evansville, Indiana 47721 U.S.A.


L-K244-1-87

# Routine VI-FLOR® supplementation

**to help you guard appropriate patients against caries risk and nutritional risk.**

INDICATIONS AND USAGE: Prophylaxis of vitamin deficiencies and dental caries in children and adults when fluoride of water supply does not exceed 0.7 ppm.[1,2,3] And, in the case of TRI-VI-FLOR® 0.25 mg Drops with Iron and POLY-VI-FLOR® Drops and Chewable Tablets with Iron, prophylaxis against iron deficiencies. Note: VI-FLOR Drops do not contain folic acid because the vitamin is not stable in liquid form.

PRECAUTIONS: Do not exceed recommended dose or give concurrently with other medications containing significant amounts of fluoride. Prolonged excessive fluoride intake may cause dental fluorosis. All VI-FLOR® with Iron products: as with all products containing iron, parents should be warned against excessive dosage. The bottle should be kept out of reach of children.

Keep all VI-FLOR with Iron products tightly closed and away from direct light.

VI-FLOR Drops should be dispensed in the original plastic container, since contact with glass leads to instability and precipitation.

ADVERSE REACTIONS: Allergic rash has rarely been reported.

DOSAGE AND ADMINISTRATION:
Supplemental Fluoride Dosage Schedule (mg/day)*

| Age | Concentration of Fluoride in Drinking Water (ppm) | | |
|---|---|---|---|
| | <0.3 | 0.3-0.7 | >0.7 |
| 2-wk-2 yr** | 0.25 | 0 | 0 |
| 2-3 yr | 0.5 | 0.25 | 0 |
| 3-16 yr | 1.0 | 0.5 | 0 |

*From the American Academy of Pediatrics Committee on Nutrition statement. Fluoride Supplementation: Revised Dosage Schedule. *Pediatrics* 63(1):150-152, 1979.
**The Committee favors initiating fluoride supplementation shortly after birth in breast-fed infants (0.25 mg F/day). In formula-fed infants, fluoride supplementation should be according to the fluoride content of the water used to prepare formula.

| PRODUCT | FORM | SIZE | FLUORIDE mg/dose |
|---|---|---|---|
| POLY-VI-FLOR 0.25 mg | Drops | 50 ml Bottle | 0.25 |
| POLY-VI-FLOR 0.25 mg with Iron | Drops | 50 ml Bottle | 0.25 |
| POLY-VI-FLOR 0.25 mg | Tablets | Bottle of 100 | 0.25 |
| POLY-VI-FLOR 0.25 mg with Iron | Tablets | Bottle of 100 | 0.25 |
| POLY-VI-FLOR 0.5 mg | Drops | 50 ml Bottle | 0.5 |
| POLY-VI-FLOR 0.5 mg with Iron | Drops | 50 ml Bottle | 0.5 |
| POLY-VI-FLOR 0.5 mg | Tablets | Bottle of 100 | 0.5 |
| POLY-VI-FLOR 0.5 mg with Iron | Tablets | Bottle of 100 | 0.5 |
| POLY-VI-FLOR 1.0 mg | Tablets | Bottle of 100 | 1.0 |
| POLY-VI-FLOR 1.0 mg with Iron | Tablets | Bottle of 100 | 1.0 |
| TRI-VI-FLOR 0.25 mg | Drops | 50 ml Bottle | 0.25 |
| TRI-VI-FLOR 0.25 mg with Iron | Drops | 50 ml Bottle | 0.25 |
| TRI-VI-FLOR 0.5 mg | Drops | 50 ml Bottle | 0.5 |
| TRI-VI-FLOR 1.0 mg | Tablets | Bottle of 100 | 1.0 |

REFERENCES:
1. Hennon DK, Stookey GK and Muhler JC: The Clinical Anticariogenic Effectiveness of Supplementary Fluoride-Vitamin Preparations—Results at the End of Four Years. *J Dentistry for Children* 34:439-443 (Nov) 1967.
2. Hennon DK, Stookey GK and Muhler JC: The Clinical Anticariogenic Effectiveness of Supplementary Fluoride-Vitamin Preparations—Results at the End of Five and a Half Years. *Pharmacology and Therapeutics in Dentistry* 1:1-6 (Oct) 1970.
3. Hennon DK, Stookey GK and Muhler JC: Prophylaxis of Dental Caries: Relative Effectiveness of Chewable Fluoride Preparations With and Without Added Vitamins. *J Pediatrics* 80:1018-1021 (June) 1972.

**VI-SOL®/VI-FLOR® products are the nation's most prescribed children's vitamin and vitamin-fluoride supplements.**

(For complete details, please consult full prescribing information.)

Mead Johnson
NUTRITIONAL DIVISION


# In Memoriam

*(Continued from Page 780)*

MARTEL, JULIUS, San Pablo. Died Mar 13, 1987, aged 57. Graduate of University of California, Irvine. Dr Martel was a member of the Alameda-Contra Costa Medical Association.

❧

MILLS, WILLIAM, Oakland. Died Mar 9, 1987, aged 91. Graduate of University of Pennsylvania School of Medicine, Philadelphia, 1920. Licensed in California in 1921. Dr Mills was a member of the Alameda-Contra Costa Medical Association.

❧

MITCHELL, ALLEN C. Died Mar 7, 1987, aged 72. Graduate of Stanford University School of Medicine, 1940. Licensed in California in 1940. Dr Mitchell was a member of the Monterey County Medical Society.

❧

O'NEIL, ALBERT A. Died Jan 21, 1987, aged 69 years. Graduate of University of Manitoba Faculty of Medicine, Winnipeg, 1943. Licensed in California in 1949. Dr O'Neil was a member of the Alameda-Contra Costa Medical Association.

❧

PILSON, MORRIS J. Died Feb 8, 1987, aged 91. Graduate of Los Angeles College of Osteopathy, 1933. Licensed in California in 1933. Dr Pilson was a member of the Los Angeles County Medical Association.

❧

RICHARDS, GEORGE M., Santa Barbara. Died Feb 21, 1987, aged 95. Graduate of Albany Medical College, Albany, New York, 1916. Licensed in California in 1951. Dr Richards was a member of the Santa Barbara County Medical Society.

❧

ROBBINS, EDWARD D., San Francisco. Died Mar 24, 1987, aged 69. Graduate of University of Chicago, 1943. Licensed in California in 1950. Dr Robbins was a member of the San Francisco Medical Society.

❧

ROBERTSON, EVALYN, Oakland. Died Jan 24, 1987, aged 56. Graduate of University of Cincinnati College of Medicine, 1960. Licensed in California in 1960. Dr Robertson was a member of the Alameda-Contra Costa Medical Association.

❧

SHEPPARD, WILLIAM B. Died Mar 28, 1987, aged 78. Graduate of Johns Hopkins University School of Medicine, 1935. Licensed in California in 1948. Dr Sheppard was a member of the Alameda-Contra Costa Medical Association.

❧

THORPE, H. HARPER. Died Jan 19, 1987, aged 70. Graduate of Northwestern University Medical School, Chicago, 1943. Licensed in California in 1946. Dr Thorpe was a member of the Shasta-Trinity County Medical Society.

❧

WILSON, RODNEY GUY. Died Mar 7, 1987, aged 73. Graduate of University of California, Irvine. Dr Wilson was a member of the Los Angeles County Medical Association.

## *New Mexico Medical Society*

BIRCH, JOHN H., Albuquerque. Died Jan 16, 1987, aged 60. Graduate of the Medical School University of Birmingham, England, 1948. Licensed in New Mexico in 1960. Dr Birch was a member of the greater Albuquerque Medical Association.

MOSELEY, ROBERT D., Albuquerque. Died Mar 12, 1987, aged 63. Graduate of Louisiana State University, New Orleans, 1947. Licensed in New Mexico in 1950. Dr Moseley was a member of the Greater Albuquerque Medical Association.

❧

OAKES, WILLIAM R., Los Alamos. Died Feb 1, 1987, aged 74. Graduate of Yale University School of Medicine, New Haven, Connecticut, 1940. Licensed in New Mexico in 1947. Dr Oakes was a member of the Los Alamos County Medical Society.

❧

TIEDEMANN, JOHN H., Belen. Died Apr 13, 1987, aged 82. Graduate of Middlesex University School of Medicine, Waltham, Mass, 1943. Licensed in New Mexico in 1965. Dr Tiedemann was a member of the Mid-Rio Grande County Medical Society.

## *Utah State Medical Association*

ELY, ROBERT S., Salt Lake City. Died Mar 5, 1987, aged 65. Graduate of University of Minnesota. Licensed in Utah in 1951. Dr Ely was a member of the Salt Lake County Medical Society.

❧

NORTON, MINTHORNE D., Price. Died Mar 19, 1987, aged 49. Graduate of University of Miami. Dr Norton was a member of the Carbon County Medical Society.


# WHY AMA?

The AMA can help you build and improve the efficiency of your practice through Practice Management seminars and audio visual courses. These programs are designed to assist you in every phase of your practice by providing you with practical information about business procedures and management techniques. Practice Management: it's one more good reason why you should be a part of the AMA.

**To Join,**
Contact your county or state medical society or write: Division of Membership, AMA, 535 North Dearborn Street, Chicago, Illinois 60610 or call collect, (312) 751-6196.

AMA
AMERICAN MEDICAL ASSOCIATION

CALIFORNIA, UNITED STATES, INTERNATIONAL

THE PROFESSIONAL RESPECT OF

A NAVAL OFFICER

# P H Y S I C I A N S

THE PRESTIGE OF

MEDICAL PRACTICE

## RESERVES

(PART-TIME)

- 2 DAYS PER MONTH
- 2 WEEKS PER YEAR
- COMMISSARY PRIVILEGES
- FULLY QUALIFIED SUPPORT STAFF
- *NO OVERHEAD EXPENSES*
- U.S. CITIZENSHIP REQUIRED
- EXTRA INCOME
- OPENING IN MOST SPECIALTIES
- *COST FREE RETIREMENT PROGRAM*

**CALL: 1 (800) 252-0538**

## REGULARS

(FULL-TIME)

- 30 DAYS ANNUAL PAID VACATION
- *COST FREE LIABILITY INSURANCE*
- U.S. CITIZENSHIP REQUIRED
- OPENINGS IN MOST SPECIALTIES
- *COST FREE ACCREDITED GRADUATE MEDICAL EDUCATION*
- NO OVERHEAD EXPENSES
- GUARANTEED INCOME
- RELOCATION EXPENSES PAID

**CALL: 1 (800) 252-0559**

**BE THE DOCTOR YOU WANT TO BE.
IN THE NAVY.**

## CONTINUING MEDICAL EDUCATION

*(Continued from Page 794)*

August 28-30—**3rd Annual Sonographers' Update and Review.** UCSD at Bahia Resort Hotel, San Diego. Fri-Sun. 16 hrs. $275. Contact: Dawne Ryals, PO Box 920113, Norcross, GA 30092-0113. (404) 641-9773.

August 29-30—**Advances in Imaging Technology.** UCSF at Hyatt Regency, San Francisco. Sat-Sun. Contact: UCSF.

September 10-12—**Contemporary Diagnostic Imaging: CT, Interventional, MRI, US.** UCSF at Hyatt Regency, Monterey. Thurs-Sat. Contact: UCSF.

September 10-12—**Advances in Sectional Imaging.** UCSD at US Grant Hotel, San Diego. Thurs-Sat. 14 hrs. $375. Contact: UCSD.

September 10-13—**Physics of Diagnostic Radiology.** UCD at UCD. Thurs-Sun. 25 hrs. Contact: UCD.

September 17-19—**Ultrasound Workshop.** UCSF at San Francisco. Thurs-Sat. Contact: UCSF.

October 17-18—**Magnetic Resonance Imaging for Technologists.** UCSF at Hyatt Regency Hotel, San Francisco. Sat-Sun. Contact: UCSF.

October 19-23—**Clinical Magnetic Resonance Imaging.** UCSF at Hyatt Regency Hotel, San Francisco. Mon-Fri. $495. Contact: UCSF.

October 19-23—**12th Annual San Diego Postgraduate Course.** UCSD at Hotel del Coronado, Coronado. Mon-Fri. 28 hrs. $425. Contact: Dawne Ryals, PO Box 920113, Norcross, GA 30092-0113. (404) 641-9773.

### SPORTS MEDICINE

July 27-31—**Sports Medicine Update—1987.** UCSD at San Diego Princess Hotel, Vacation Village. Mon-Fri. 29.5 hrs. $325. Contact: UCSD.

### SURGERY

September 14-17—**Cochlear Implant Training—1987.** House Ear Institute, Los Angeles. Mon-Thurs. 24 hrs. $250. Contact: Antonio De la Cruz, MD, House Ear Institute, 256 S Lake St, Los Angeles 90057. (213) 483-4431.

October 4-10—**Temporal Bone Surgical Dissection.** House Ear Institute, Los Angeles. Sun-Sat. $750-950. Contact: Antonio De la Cruz, MD, Director of Education, House Ear Institute, 256 S Lake St, Los Angeles 90057. (213) 483-4431.

October 18-24—**Temporal Bone Surgical Dissection—1987.** House Ear Institute, Los Angeles. Sun-Sat. $750-950. Contact: Antonio De la Cruz, MD, Director of Education, House Ear Institute, 256 S Lake St, Los Angeles 90057. (213) 483-4431.

### OF INTEREST TO ALL PHYSICIANS

June 15-19—**Sexually Transmitted Disease (STD) Clinician Training Course—Advanced.** Long Beach Health Dept at Long Beach. Mon-Fri. Contact: Anne-Renee Heningberg, Long Beach STD Trng Ctr, PO Box 6157, Long Beach 90806. (213) 427-7421.

June 19-21—**Family Practice Update.** USC at Pasadena Hilton Hotel, Pasadena. Fri-Sun. 16 hrs. $250. Contact: USC.

June 26—**Mucosal Injury, Esophageal Dysfunction, and Sleep Disorders.** Sequoia Hospital District, Redwood City. Fri. 7 hrs. $110. Contact: Daniel Liebowitz, MD, Sequoia Hospital, Whipple and Alameda, Redwood City 94062. (800) 345-0409.

June 28-29—**9th Annual Poison Control Center: Management of Drug Overdose and Poisoning.** UCSF at San Francisco. Sun-Mon. 14 hrs. $235. Contact: UCSF.

*(Continued on Page 798)*

CONTINUING MEDICAL EDUCATION

(Continued from Page 797)

June 28-July 2—**Advances in Primary Care: 14th Annual Family Practice Refresher Course.** UCD at Caesar's Tahoe, So Lake Tahoe. Sun-Thurs. 25 hrs. $340. Contact: UCD.

June 30-July 6—**1987 Update on AIDS and Hepatitis: A Multidisciplinary Conference.** University of Hawaii at Royal Waikoloa Resort Hotel, The Big Island, Hawaii. Tues-Mon. 25 hrs. Contact: Stacey W. Grace, Program Director, Reed Research Institute, 250 Arapahoe Ave, Ste 303, Boulder, CO 80302. (800) 647-9593.

July 6-9—**Family Practice Board Review.** UCSF at UCSF. Mon-Thurs. 25 hrs. $375. Contact: UCSF.

August 6-9—**Skills Update—II.** American Association of Sex Educators, Counselors and Therapists at Las Vegas, Nevada. Thurs-Sun. 18 hrs. $150. Contact: William Stull, AASECT Conferences, 2333 N 3rd St, Phoenix, AZ 85004. (602) 252-2706.

August 16-26—**30th Anniversary Postgraduate Refresher Course—Program I.** USC at Sheraton Waikiki Hotel, Honolulu and the Marriott Hotel, Maui, Hawaii. Sun-Wed. 37 hrs. $535-585. Contact: USC, in California, (800) 321-1919, outside California, (800) 421-6729.

August 20-21—**6th Annual: General Medicine Update for Practicing Physicians.** Northern Inyo Hospital, Bishop. Wed-Thurs. 10 hrs. Contact: Lynda Schmidt, Northern Inyo Hosptial, 150 Pioneer Lane, Bishop 93514. (619) 873-5811.

August 23-September 2—**30th Anniversary Postgraduate Refresher Course—Program II.** USC at Marriott Hotel, Maui and the Waiohai Hotel, Kaui, Hawaii. Sun-Wed. 37 hrs. $535-585. Contact: USC, in California, (800) 321-1929, outside California, (800) 421-6729.

August 30—**1 Day Dermatology and Dermatologic Office Procedures Workshop.** Continuing Medical Education Associates at Newporter Resort, Newport Beach. Sun. 7 hrs. $195. Contact: J. Shiller, CMEA, PO Box 84296, San Diego 92138. (619) 223-2997.

September 9-11—**Primary Care Medicine: Principles and Practice.** UCSF at Hyatt on Union Square, San Francisco. Wed-Fri. 20 hrs. $365. Contact: UCSF.

September 13—**1 Day Dermatology and Dermatologic Office Procedures Workshop.** Continuing Medical Education Associates at Holiday Inn Union Square, San Francisco. Sun. 7 hrs. $195. Contact: J. Shiller, CMEA, PO Box 84296, San Diego 92138. (619) 223-2997.

September 14-18—**STD Clinician Training Course—Intensive.** Long Beach Health Dept. Mon-Fri. Contact: Anne-Renee Heningberg, Long Beach STD Training Center, PO Box 6157, Long Beach 90806. (213) 427-7421.

September 20—**1 Day Dermatology and Dermatologic Office Procedures Workshop.** Continuing Medical Education Associates at Hyatt Islandia Hotel, San Diego. Sun. 7 hrs. $195. Contact: J. Shiller, CMEA, PO Box 84296, San Diego 92138. (619) 223-2997.

September 21-22—**7th Annual Bristol-Myers Symposium on Nutrition Research: Nutrition and the Origins of Disease.** UCD at Fairmont Hotel, San Francisco. Mon-Tues. Contact: UCD.

October 16-18—**Office Orthopedics for the Primary Care Physician.** Sharp Memorial Hospital at San Diego Princess Hotel. Fri-Sun. 20 hrs. $365. Contact: J. Shiller, CMEA, PO Box 84296, San Diego 92138. (619) 223-2997.

October 19-22—**Annual Family Practice Update.** Mon-Thurs. LLU at LLU. Contact: LLU.

October 19-30—**Sexually Transmitted Disease (STD) Clinician Training Course—Comprehensive.** Long Beach Health Department and UCI at Long Beach. Mon-Fri. Anne-Renee Heningberg, Long Beach STD Training Center, PO Box 6157, Long Beach 90806. (213) 427-7421.

October 26-November 1—**Traumatic Brain Injury.** UCD at Red Lion Motor Inn, Sacramento. Mon-Sun. Contact: UCD.

## IDAHO

June 28-July 5—**Effective Management of Common Sports Injuries.** Middle Fork of the Salmon River. One week. Sponsored by the University of Arizona College of Medicine, Department of Family and Community Medicine, and Epic Expeditions. 24 hrs. Contact: Kathy Rairigh, EPIC EXPEDITIONS, PO Box 209, Sun Valley, ID 83353. (208) 788-4995.

July 27-August 2—**Idaho Medical Association Annual Meeting.** Coeur d'Alene. One week. Contact: IMA, 305 W Jefferson, PO Box 2668, Boise 83701. (208) 344-7888.

August 1-8—**Forefronts in Pediatrics.** Sun Valley. One week. Sponsored by the University of Arizona College of Medicine, Department of Family and Community Medicine, and Epic Expeditions. 24 hrs. Contact: Kathy Rairigh, EPIC EXPEDITIONS, PO Box 209, Sun Valley, ID 83353. (208) 788-4995.

August 13-15—**Sun Valley Emergency Medical Conference.** Convention Center, Sun Valley. Thurs-Sat. Contact: Idaho EMS System, 450 W State St, Boise 83720. (208) 334-5994.

## MONTANA

June 18-20—**Montana Academy of Family Physicians—Annual Meeting.** Fairmont Hot Springs, Anaconda. 17 hrs. Contact: John Patterson, MD, 7 E Beall, Bozeman 59715. (406) 587-5123.

August 3-5—**Rocky Mountain Rural Trauma Symposium** (Sponsors: University of Washington School of Medicine, Montana State University, Montana Committee on Trauma, Montana EMS Bureau). Montana State University, Bozeman. Mon-Wed. 17 hrs. $350. Contact: Continuing Education for the Health Professional, 303 Montana Hall, Montana State University, Bozeman 59717. (406) 994-4930.

## NEW MEXICO

Information, requests for accreditation and items to be listed should be sent to the chairman of the CME Committee, New Mexico Medical Society, 303 San Mateo NE, Suite 204, Albuquerque, NM 87108 at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 266-7868.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

June 25-27—**General Surgical Update.** Albuquerque. Thurs-Sat. Marriott Hotel. Contact: Office of Continuing Medical Education, UNM School of Medicine, Albuquerque 87131. (505) 277-3942.

June 23-28—**New Mexico Osteopathic Medical Association Annual Meeting.** Albuquerque. Tues-Sun. Pyramid Hotel. Contact: NMOMA, PO Box 3096, Albuquerque 87110. (505) 884-0201.

July 9-11—**New Mexico Ophthalmological Society Annual Meeting.** Hotel Eldorado, Santa Fe. Thurs-Sat. Contact: Donald J. Ham, MD, (505) 434-1200.

July 20-23—**Annual Ruidoso Family Practice Seminar.** Inn of the Mountain Gods, Mescalero. Mon-Thurs. Contact: NM Chapter, AAFP, PO Box 23070, Albuquerque 87192. (505) 298-5300.

July 24-25—**Santa Fe Cardiology Symposium.** Santa Fe. Fri-Sat. Contact: Richard D. Lueker, MD, 909 Virginia NE, #202, Albuquerque 87108. (505) 255-8474.

September 24-26—**Wilson Lectureship—Cardiology Symposium.** Albuquerque. Thurs-Sat. Contact: Presbyterian Heart Institute Cardiology Symposium, PO Box 26666, Albuquerque 87125. (505) 841-1065.

(Continued on Page 800)

# )LC Diagnostics Offers
# Blood Chemistry and Hematology Testing
## in your own office *NOW!*

DLC provides complete
installation and training.

## :ELL–DYN HEMATOLOGY ANALYZERS

**he ultimate in low cost hematology testing.**
**n invitation to join thousands of satisfied customers.**

/e offer a complete line of economical
:ELL-DYN hematology instruments
esigned to fill any cell counter need.
:ELL-DYN analyzers use one-touch
iscrete testing and incorporate
ser-friendly programming. Choosing
:ELL-DYN insures reliability. A recent
urvey of over 1500 CELL-DYN instruments
)icked randomly) indicated an amazing
12 days between customer-requested
ervice calls. Now that's reliability you
an depend on!

## ASCA BLOOD CHEMISTRY ANALYZER

**The first "proven" centrifugal random access chemistry analyzer with a 3-year track record of uncommon accuracy and reliability.**

ASCA can perform more than 70 chemistry tests including thyroids, drugs and special chemistries, with any number of 36 general chemistry methodologies performed simultaneously.

- Low initial cost.
- Re-usable 40-place carousel.
- Average test cost of 8¢!
- Over 70 chemistries available.
- 480 end points or 400 kinetics per hour in the batch mode.
- Batch, Stat or Profile modes with results in less than 8 minutes.

Call DLC Diagnostics • California/Nevada Distributors
In California **(800) 858-3889** • Out-Of-State Call Collect **(213) 602-2184**
7008 Marcelle Street • Paramount, California 90723

(Continued from Page 798)

# UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the CME office of the Utah State Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. They also must meet the definition of Utah Approved CME Credit for the purpose of medical license reregistration in Utah. Accredited institutions wishing to list AMA Category 1/Utah Approved CME courses here should send information at least two months in advance to the Office of Continuing Medical Education, 540 East Fifth South, Salt Lake City, Utah 84102; or phone (801) 355-5290. For information on CME accreditation or on the CME requirements of the Utah Physicians' Licensing Board, please write the CME office at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution or the CME office for current details.

## MEDICAL GRAND ROUNDS

Each Wed—8:00-9:00 a.m. Alternating between University of Utah Medical Center and VA Medical Center, Salt Lake City. Contact: William D. Odell, MD, PhD, Professor and Chairman, Dept of Internal Medicine, Univ of Utah, (801) 581-7606.

* * *

### SPONSORS OF COURSES—ABBREVIATIONS

AHA: American Heart Association, Utah Affiliate, 645 E 400 South, Salt Lake City 84102. (801) 322-5601.

BYUHS: Brigham Young University Health Services, McDonald Student Health Center, Brigham Young University, Provo 84602. (801) 378-2771.

CH: Castleview Hospital (formerly Carbon Hospital), RFD 2, Box 46, Price 84501. (801) 637-4800.

CWH: Cottonwood Hospital, 5770 S 300 East, Salt Lake City 84101. (801) 262-3461.

DMC: Dixie Medical Center, 544 S 400 East, St George 84770. (801) 673-9681.

HCH: Holy Cross Hospital, 1045 E First South, Salt Lake City 84102. (801) 350-4744.

ITS: Intermountain Thoracic Society, 1616 S 11th East, Salt Lake City 84105. (801) 484-4456.

LDSH: Latter-Day Saints Hospital, 325 8th Ave, Salt Lake City 84143. (801) 350-1100.

LRH: Logan Regional Hospital, 1400 N 5th East, Logan 84321. (801) 752-2050.

MDH: McKay-Dee Hospital Center, 3939 Harrison Blvd, Ogden 84409. (801) 399-4141.

MVH: Mountain View Hospital, 1000 E Highway 6, Payson 84651. (801) 465-9201.

144: 144th Evacuation Hospital, PO Box 8000, Salt Lake City 84108. (801) 524-3924.

OSS: Ogden Surgical Society, PO Box 9311, Ogden 84409.

PCMC: Primary Children's Medical Center, 320 12th Ave, Salt Lake City 84103. (801) 363-1221.

PVH: Pioneer Valley Hospital, 3460 S 4155 West, West Valley City 84120. (801) 968-9061.

SMH: St Mark's Hospital, 1200 E 3900 South, Salt Lake City 84117. (801) 268-7111.

UOS: Utah Ophthalmological Society, 540 E 500 South, Salt Lake City 84102. (801) 355-7477.

USH: Utah State Hospital, PO Box 270, Provo 84603-0270. (801) 373-4400.

UUMC: University of Utah Medical Center, 50 N Medical Dr, Salt Lake City 84132. (801) 581-2258.

UVH: Utah Valley Hospital, 1034 N Fifth West, Provo 84601. (801) 373-7850.

VAMC: Veterans Administration Medical Center, 500 Foothill Dr, Salt Lake City 84148. (801) 582-1565.

VVMC: Valley View Medical Center, 595 S 75 East, Cedar City 84720. (801) 586-6587.

August 24-28—**Occupational Epidemiology** (Sponsor: UUMC). Mon-Fri. College of Nursing, Univ of Utah, Salt Lake City. 32.5 hrs. Contact: Connie Crandall, (801) 581-5710.

August 31-September 4—**Environmental Epidemiology and Risk Assessment** (Sponsor: UUMC). Mon-Fri. College of Nursing, Univ of Utah, Salt Lake City. 32.5 hrs. Contact: Connie Crandall, (801) 581-5710.

September 9-11—**Utah State Medical Association Annual Meeting.** Marriott Hotel, Salt Lake City. Wed-Fri. Contact: USMA, 540 E Fifth South, Salt Lake City 84102. (801) 355-5290.

# WASHINGTON

This listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. To list Category 1 programs here please send information at least two months in advance to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 900, Seattle, WA 98121; or phone (206) 441-WSMA.

Brochures and registration forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

June 17-19—**Family Violence.** Seattle. Wed-Fri. Kane Hall, U/W. Contact: U/W.

June 25-26—**Infectious Diseases.** Seattle. Thurs-Fri. Holiday Inn Crowne Plaza. Contact: (206) 364-0500, #1621.

July 19-23—**Reducing Risks From Environmental Chemicals Through Biotechnology.** Seattle. Sun-Thurs. NW Center for Occupational Health and Safety. Contact: U/W.

July 24-26—**WSSA: Seafair IX Regional Anesthesia.** Seattle. Fri-Sun. Virginia Mason Medical Center. Contact: VMMC.

October 1-2—**American College of Emergency Physicians—17th Annual Fall Scientific Assembly.** Seattle. Thurs-Fri. Bellevue Red Lion Inn. Contact: Washington Chap, ACEP, (206) 441-9762.

### COURSE SPONSORS AND CONTACT INFORMATION

CME HARBORVIEW—Contact: Gayle Splater, Cytology Continuing Education, Dept. of Pathology, Harborview Medical Center, 325 Ninth Avenue, Seattle, WA 98104. (206) 223-5953.

CME PIERCE COUNTY—Contact: Mrs Maxine Bailey, Executive Director, College of Medical Education, 705 South Ninth, No. 203, Tacoma, WA 98405. (206) 627-7137.

U/W (UNIVERSITY OF WASHINGTON)—Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

WSMA—Washington State Medical Association, Continuing Medical Education, 2033 Sixth Ave, Suite 900, Seattle, WA 98121. (206) 441-9762.

VMMC (VIRGINIA MASON MEDICAL CENTER)—Contact: Linda Orgel, Division of Continuing Medical Education, Virginia Mason Medical Center, PO Box 900, Seattle, WA 98111. (206) 223-6898.

# WYOMING

June 25-29—**Wyoming Medical Society Annual Meeting.** Jackson Lake Lodge, Moran. Thurs-Mon. Contact: WMS, PO Drawer 4009, Cheyenne 82003-4009. (307) 635-2424.

June 28-July 2—**Update on General Pediatrics.** University of Nebraska College of Medicine at Jackson Hole Racquet Club, Jackson. Sun-Thurs. Contact: Brenda Ram, Center for Continuing Education, Univ of Nebraska Medical Center, 42nd and Dewey Ave, Omaha, NE 68105. (402) 559-4152.

July 5-9—**Sports Medicine Update 1987.** University of Nebraska College of Medicine at Jackson Hole Racquet Club, Jackson. Sun-Thurs. Contact: Brenda Ram, Center for Continuing Education, Univ of Nebraska Medical Center, 42nd and Dewey Ave, Omaha, NE 68105. (402) 559-4152. ◆

# AN INVITATION TO THE COEUR D'ALENE JULY 29-AUGUST 1, 1987

We are pleased to extend to you a cordial invitation to attend the 95th Annual Meeting of the Idaho Medical Association at the beautiful Coeur d'Alene Resort on the lake. An excellent scientific session has been planned that should appeal to all physicians. It should be a good opportunity not only to enjoy northern Idaho on one of the country's most beautiful lakes, but also receive 8 CME credit hours of Category I at an informative scientific session.

**JULIAN O. NICHOLSON, MD, PRESIDENT**
IDAHO MEDICAL ASSOCIATION

## 95th ANNUAL MEETING—IDAHO MEDICAL ASSOCIATION

### WEDNESDAY, JULY 29, 1987

**9 am to 5 pm** **HOUSE OF DELEGATES**

### THURSDAY, JULY 30
### SCIENTIFIC SESSION

**7:30 am** **BIOLOGIC CONTROL OF CANCER**
John Thompson, MD
University of Washington, Division of Oncology

**9:30 am** **CANCER PAIN**
George Khoury, MD
UCLA Cancer Pain Clinic, UCLA Anesthesiology Dept., Los Angeles, California

**11:00 am** **CURRENT STATUS OF VIRUS TREATMENT**
Ann Collier, MD
Harborview Medical Center, Seattle, Washington

**1:30 pm** **ALTERNATIVE THERAPIES**
Paul Wassermann, MD
Scottsdale Clinic, Division of Oncology

**2:30 pm** **WHERE ARE WE GAINING IN THE BATTLE AGAINST CANCER?**
John Thompson, MD

**3:30 pm** **SCREENING FOR CANCER, WHERE DOES IT PAY?**
Paul Wassermann, MD

### FRIDAY, JULY 31
### SCIENTIFIC SESSION

**8:30 am** **ONCOLOGIC IMAGING IN DIAGNOSIS AND STAGING**
Charles Carrasco, MD
St. Luke's Hospital, Boise, Idaho

**10:00 am** **MAMMOGRAPHIC SCREENING—IS IT WORTH THE TROUBLE?**
Jake Meighan, MD
Inland Imaging, Spokane, Washington

Father Bill Wassmuth, Chairman, Kootenai County Task Force on Human Relations, will address the IMA Auxiliary this morning

### SATURDAY, AUGUST 1

**8:30 am** **CLOSING SESSION, HOUSE OF DELEGATES**

**Registration Fee**—$150 for non-IMA members and out-of state physicians.
**For Information Contact:** Idaho Medical Association, PO Box 2668
Boise, ID 83701
Telephone: (208) 344-7888

# Check our vital signs.

More physicians in California depend upon SCPIE than any other company for their professional liability insurance. There are many reasons why SCPIE is the leader. Check them out:

**Rates:** This is your bottom line. SCPIE rates are highly competitive. "Profits" are returned to the policyholders through Experience Credits.

**Stability:** SCPIE has a history of stable rates and financial strength. SCPIE has adequate reserves to pay anticipated claims, plus surplus to cover unexpected losses. SCPIE is reinsured with Lloyds of London.

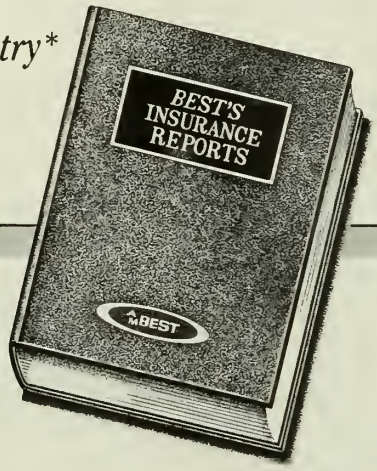
**Non-assessability:** You cannot be assessed if claims experience turns sour. SCPIE is a top-flight *insurance* company, not a cooperative which requires you to assume unlimited liability for others' losses.

**Claims Handling:** A claim is a traumatic experience. You get highly qualified legal counsel, experienced in professional liability claims. Three out of four claims are closed without payment. Our record of defense verdicts is over 85%.

**Underwriting:** Physicians review all applications requesting nose coverage and/or with claims history. SCPIE also maintains an on-going underwriting process to be sure members meet quality standards.

**Local physician control:** SCPIE is owned by its physician policyholders, who elect physicians to run it. They make sure that overhead is low and performance is high.

*A+ Rating from A.M. Best Company, the Bible of the insurance industry**




* *SCPIE is one of only five physician-owned companies in the nation to have the Best's A+ rating. We are the largest of them all.*

scpie

Southern California Physicians Insurance Exchange

2029 Century Park East
Suite 2300
Los Angeles, CA 90067
(213) 552-8900

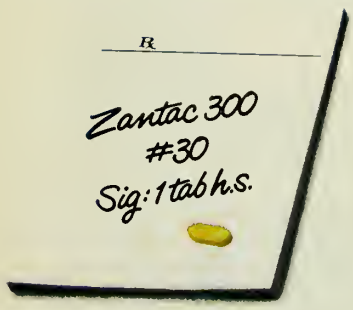
Sponsored by SOCAP: The medical associations and societies of Kern County, Los Angeles County, Orange County, San Bernardino County, San Luis Obispo County, Santa Barbara County and Ventura County.

CONTROL
ACID RAIN
with once-a-night
h.s. therapy for active
duodenal ulcers
Zantac 300
ranitidine HCl/Glaxo 300 mg tablets
Glaxo
ROCHE
See adjacent page for Brief Summary
of Product Information

*In active duodenal ulcers*

# Once-a-night h.s. therapy controls acid rain

**Zantac® 300**
ranitidine HCl/Glaxo 300 mg tablets




**ZANTAC® 150 Tablets**
**(ranitidine hydrochloride)**
**ZANTAC® 300 Tablets**
**(ranitidine hydrochloride)**

**BRIEF SUMMARY OF PRODUCT INFORMATION**

The following is a brief summary only. Before prescribing, see complete prescribing information in ZANTAC® product labeling.

**INDICATIONS AND USAGE:** ZANTAC® is indicated in:

1. Short-term treatment of **active duodenal ulcer.** Most patients heal within four weeks.
2. **Maintenance therapy** for duodenal ulcer patients at reduced dosage after healing of acute ulcers.
3. The treatment of **pathological hypersecretory conditions** (eg, Zollinger-Ellison syndrome and systemic mastocytosis).
4. Short-term treatment of **active, benign gastric ulcer.** Most patients heal within six weeks and the usefulness of further treatment has not been demonstrated.
5. Treatment of **gastroesophageal reflux disease (GERD).** Symptomatic relief commonly occurs within one or two weeks after starting therapy and is maintained throughout a six-week course of therapy.

In active duodenal ulcer; active, benign gastric ulcer; hypersecretory states; and GERD, concomitant antacids should be given as needed for relief of pain.

**CONTRAINDICATIONS:** ZANTAC® is contraindicated for patients known to have hypersensitivity to the drug.

**PRECAUTIONS:** Symptomatic response to ZANTAC® therapy does not preclude the presence of gastric malignancy.

Since ZANTAC is excreted primarily by the kidney, dosage should be adjusted in patients with impaired renal function (see **DOSAGE AND ADMINISTRATION**). Caution should be observed in patients with hepatic dysfunction since ZANTAC is metabolized in the liver.

False-positive tests for urine protein with Multistix® may occur during ZANTAC therapy, and therefore testing with sulfosalicylic acid is recommended.

Although recommended doses of ZANTAC do not inhibit the action of cytochrome P-450 enzymes in the liver, there have been isolated reports of drug interactions which suggest that ZANTAC may affect the bioavailability of certain drugs by some mechanism as yet unidentified (eg, a pH-dependent effect on absorption or a change in volume of distribution).

Lack of experience to date precludes recommending ZANTAC for use in children or pregnant patients. Since ZANTAC is secreted in human milk, caution should be exercised when administered to a nursing mother.

**ADVERSE REACTIONS:** Headache, sometimes severe, seems to be related to ZANTAC® administration. Constipation, diarrhea, nausea/vomiting, and abdominal discomfort/pain have been reported. There have been rare reports of malaise, dizziness, somnolence, insomnia, vertigo, tachycardia, bradycardia, premature ventricular beats, and arthralgias. Rare cases of reversible mental confusion, agitation, depression, and hallucinations have been reported, predominantly in severely ill elderly patients.

In normal volunteers, SGPT values were increased to at least twice the pretreatment levels in 6 of 12 subjects receiving 100 mg qid IV for seven days, and in 4 of 24 subjects receiving 50 mg qid for five days. With oral administration there have been occasional reports of reversible hepatitis, hepatocellular or hepatocanalicular or mixed, with or without jaundice.

There have been rare reports of reversible leukopenia, granulocytopenia, thrombocytopenia, and pancytopenia.

Although controlled studies have shown no antiandrogenic activity, occasional cases of gynecomastia, impotence, and loss of libido have been reported in male patients receiving ZANTAC, but the incidence did not differ from that in the general population.

Incidents of rash, including rare cases suggestive of mild erythema multiforme, and, rarely, alopecia, have been reported, as well as rare cases of hypersensitivity reactions (eg, bronchospasm, fever, rash, eosinophilia) and small increases in serum creatinine.

**OVERDOSAGE:** Information concerning possible overdosage and its treatment appears in the full prescribing information.

**DOSAGE AND ADMINISTRATION: Active Duodenal Ulcer:** The current recommended adult oral dosage is 150 mg twice daily. An alternate dosage of 300 mg once daily at bedtime can be used for patients in whom dosing convenience is important. The advantages of one treatment regimen compared to the other in a particular patient population have yet to be demonstrated.

**Maintenance Therapy:** The current recommended adult oral dosage is 150 mg at bedtime.

**Pathological Hypersecretory Conditions (such as Zollinger-Ellison Syndrome):** The current recommended adult oral dosage is 150 mg twice a day. In some patients it may be necessary to administer ZANTAC 150-mg doses more frequently. Doses should be adjusted to individual patient needs, and should continue as long as clinically indicated. Doses up to 6 g/day have been employed in patients with severe disease.

**Benign Gastric Ulcer:** The current recommended adult oral dosage is 150 mg twice a day.

**GERD:** The current recommended adult oral dosage is 150 mg twice a day.

**Dosage Adjustment for Patients with Impaired Renal Function:** On the basis of experience with a group of subjects with severely impaired renal function treated with ZANTAC, the recommended dosage in patients with a creatinine clearance less than 50 ml/min is 150 mg every 24 hours. Should the patient's condition require, the frequency of dosing may be increased to every 12 hours or even further with caution. Hemodialysis reduces the level of circulating ranitidine. Ideally, the dosage schedule should be adjusted so that the timing of a scheduled dose coincides with the end of hemodialysis.

**HOW SUPPLIED:** ZANTAC® 300 Tablets (ranitidine hydrochloride equivalent to 300 mg of ranitidine) are yellow, capsule-shaped tablets embossed with "ZANTAC 300" on one side and "Glaxo" on the other. They are available in bottles of 30 (NDC 0173-0393-40) and unit dose packs of 100 tablets (NDC 0173-0393-47).

ZANTAC® 150 Tablets (ranitidine hydrochloride equivalent to 150 mg of ranitidine) are white tablets embossed with "ZANTAC 150" on one side and "Glaxo" on the other. They are available in bottles of 60 tablets (NDC 0173-0344-42) and unit dose packs of 100 tablets (NDC 0173-0344-47).

**Store between 15° and 30°C (59° and 86°F) in a dry place. Protect from light. Replace cap securely after each opening.**

© Copyright 1983, Glaxo Inc. All rights reserved. October 1986

**Glaxo**
Glaxo Inc.
Research Triangle Park, NC 27709

The Western Journal of Medicine

SINCE 1902 • CIRCULATION 53,000+

# Classified Advertisements

The rate for each insertion is **$6 per line** (average six words per line) **with five line ($30) minimum.** Box number charge: $5 each month.

**Classified display rates $50 per inch.**

**Classified advertisements for commercial products or services—minimum charge $200.**

Copy for classified advertisements should be received not later than **25th of second month preceding issue. All copy must be typed or printed.** • Classified advertisers using Box Numbers forbid the disclosure of their identity; your inquiries in writing will be forwarded to Box Number advertisers. The right is reserved to reject or modify all classified advertising copy in conformity with the decisions of the Advertising Committee.

**Please Type or Print Advertising Copy**

## Classified Advertisements Are Payable in Advance

CLASSIFIED ADVERTISING
THE WESTERN JOURNAL OF MEDICINE
P.O. BOX 7602, SAN FRANCISCO, CA 94120-7602

## ad copy

Print or Type Clearly

Number of lines _____ × $6 = $_____

Optional: Box charge: +$5 = _____

**Subtotal (minimum $35)** $_____

Number of insertions _____ × $_____ = (subtotal)

**Check enclosed for:** $_____

Name (Please Print)

Contact

Address

City/State/Zip

(_____)_____

Phone

Signature

## WESTERN STATE MEDICAL ASSOCIATIONS' MEETINGS

**Alaska State Medical Association**—2401 E 42nd Ave, Suite 104, Anchorage 99508. (907) 562-2662. Annual Meeting: June 3-7, 1987, Juneau.

**Arizona Medical Association, Inc**—810 W Bethany Home Rd, Phoenix 85013. (602) 246-8901. Annual Meeting: June 4-6, 1987, Pointe South Mountain, Phoenix.

**California Medical Association**—PO Box 7690, San Francisco 94120-7690. (415) 863-5522. Annual Meeting: March 4-9, 1988, Bally's Grand Hotel, Reno.

**Colorado Medical Society**—PO Box 17550, Denver 80217-0550. (303) 779-5455. Annual Meeting: September 9-12, 1987, Beaver Run, Breckenridge.

**Hawaii Medical Association**—320 Ward Ave, Suite 200, Honolulu 96814. (808) 536-7702. Annual Meeting: October 10-12, 1987, Kauai Surf, Kauai.

**Idaho Medical Association**—305 W Jefferson, PO Box 2668, Boise 83701. (208) 344-7888. Annual Meeting: July 27-August 2, 1987, Coeur d'Alene.

**Montana Medical Association**—2012 11th Ave, Suite 12, Helena 59601. (406) 443-4000. Annual Meeting: October 1-3, 1987, Copper King Inn, Butte.

**Nevada State Medical Association**—3660 Baker Lane, Reno 89502. (702) 825-6788. Annual Meeting: 1988, date and place to be announced.

**New Mexico Medical Society**—303 San Mateo NE, Suite 204, Albuquerque 87108. (505) 266-7868. Annual Meeting: 1988, data and place to be announced.

**Oregon Medical Association**—5210 SW Corbett Ave, Portland 97201. (503) 226-1555. Annual Meeting: (House of Delegates only): 1988, date and place to be announced.

**Utah State Medical Association**—540 E Fifth South, Salt Lake City 84102. (801) 355-5290. Annual Meeting: September 9-11, 1987, Marriott Hotel, Salt Lake City.

**Washington State Medical Association**—900 United Airlines Bldg, 2033 6th Ave, Seattle 98121. (206) 441-WSMA. Annual Meeting: September 17-20, 1987, Sheraton, Tacoma.

**Wyoming Medical Society**—PO Drawer 4009, Cheyenne 82003-4009. (307) 635-2424. Annual Meeting: June 25-29, 1987, Jackson Lake Lodge, Moran.

## ADVERTISING INDEX


ABBOTT LABORATORIES
*Depakote* . . . . . 661, 662
AMERICAN MEDICAL ASSOCIATION . . . . . 663, 796
AUDIO DIGEST . . . . . 665
CIBA PHARMACEUTICAL COMPANY
*Transderm-Nitro* . . . . . 779, 780
CLASSIFIED ADVERTISING . . . . 778, 782, 789, 790, 792
CNA INSURANCE . . . . . 693
COOPERATIVE OF AMERICAN PHYSICIANS . . . . . 781
CURTIS INFORMATION SYSTEMS . . . . . 777
DLC DIAGNOSTICS . . . . . 799
THE DOCTORS' COMPANY . . . . . 674
ELI LILLY & COMPANY
*Ceclor* . . . . . 677
FAMILY PRACTICE RECERTIFICATION . . . . . 794
FHP PROFESSIONALS . . . . . 782
GEIGY PHARMACEUTICALS
*Lopressor* . . . . . 685, 686
GENERAL MED . . . . . 660
GLAXO
*Trandate* . . . . . 678, 679, 680
*Zantac* . . . . . 803, 804
HOFFMANN-LA ROCHE LABORATORIES
*Dalmane* . . . . . 2nd cover, 659, 660
*Rocephin* . . . . . 3rd and 4th covers
IDAHO MEDICAL ASSOCIATION . . . . . 801
MARION LABORATORIES
*Cardizem* . . . . . 675, 676
MEAD JOHNSON
*Vi-Flor* . . . . . 795, 796
MONTANA STATE UNIVERSITY . . . . . 692
PHYSICIANS PRACTICE MANAGEMENT . . . . . 785
A. H. ROBINS COMPANY
*Micro-K* . . . . . 666
SCHERING CORPORATION
*Normodyne* . . . . . 786, 787, 788
SMITHKLINE BECKMAN
*Dyazide* . . . . . 694
SOCIAL SECURITY ADMINISTRATION . . . . . 791
SOUTHERN CALIFORNIA PHYSICIANS
INSURANCE EXCHANGE . . . . . 802
E. R. SQUIBB & SONS
*Capoten* . . . . . 668, 669, 670
SYSTEMS PLUS INC. . . . . 689
SYZYGY COMPUTER SYSTEMS, INC. . . . . 673
UNIVERSITY MICROFILM . . . . . 684, 792
UNITED STATES AIR FORCE RESERVE . . . . . 684
UNITED STATES NAVY . . . . . 797
UPJOHN COMPANY
*Medrol* . . . . . 687
*Motrin* . . . . . 690, 691, 692
*Xanax* . . . . . 682, 683, 684
THE WESTERN JOURNAL OF MEDICINE
*Subscription Information* . . . . . 681
*Special Issues* . . . . . 783
WYOMING MEDICAL SOCIETY . . . . . 793


0215

# Rocephin® IV·IM

## ceftriaxone sodium/Roche

**Before prescribing, please consult complete product information, a summary of which follows:**

*MICROBIOLOGY*: The bactericidal activity of ceftriaxone results from inhibition of cell wall synthesis. Ceftriaxone has a high degree of stability in the presence of beta-lactamases, both penicillinases and cephalosporinases, of gram-negative and gram-positive bacteria. Ceftriaxone is usually active against the following microorganisms *in vitro* and in clinical infections (see Indications and Usage):

*GRAM-NEGATIVE AEROBES*: *Enterobacter aerogenes, Enterobacter cloacae, Escherichia coli, Haemophilus influenzae* (including ampicillin-resistant strains), *H parainfluenzae, Klebsiella* species (including *K pneumoniae*), *Neisseria gonorrhoeae* (including penicillinase and nonpenicillinase producing strains), *Neisseria meningitidis, Proteus mirabilis, Proteus vulgaris, Morganella morganii* and *Serratia marcescens*.

Note: Many strains of the above organisms that are multiply-resistant to other antibiotics, *e.g.* penicillins, cephalosporins and aminoglycosides, are susceptible to ceftriaxone sodium.

Ceftriaxone is also active against many strains of *Pseudomonas aeruginosa*.

*GRAM-POSITIVE AEROBES*: *Staphylococcus aureus* (including penicillinase producing strains) and *Staphylococcus epidermidis* (Note: methicillin-resistant staphylococci are resistant to cephalosporins, including ceftriaxone), *Streptococcus pyogenes* (Group A beta hemolytic streptococci), *Streptococcus agalactiae* (Group B streptococci) and *Streptococcus pneumoniae* (Note: Most strains of enterococci, *Streptococcus faecalis* and Group D streptococci are resistant.)

Ceftriaxone also demonstrates *in vitro* activity against the following microorganisms, although the clinical significance is unknown.

*GRAM-NEGATIVE AEROBES*: *Citrobacter freundii, Citrobacter diversus, Providencia* species (including *Providencia rettgeri*), *Salmonella* species (including *S typhi*), *Shigella* species and *Acinetobacter calcoaceticus*.

*ANAEROBES*: *Bacteroides* species, *Clostridium* species (Note: most strains of *C difficile* are resistant).

*SUSCEPTIBILITY TESTING*: Standard susceptibility disk method. Quantitative methods that require measurement of zone diameters give the most precise estimate of antibiotic susceptibility. One such procedure (Bauer AW, Kirby WMM, Sherris JC, Turck M: Antibiotic Susceptibility Testing by a Standardized Single Disk Method, *Am J Clin Pathol* 45: 493-496, 1966; Standardized Disk Susceptibility Test; *Federal Register* 39: 19182-19184, 1974; National Committee for Clinical Laboratory Standards, Approved Standard ASM 2, Performance Standards for Antimicrobial Disk Susceptibility Tests, July 1975) has been recommended for use with disks to test susceptibility to ceftriaxone.

Laboratory results of the standardized single-disk susceptibility test using a 30 mcg ceftriaxone disk should be interpreted according to the following three criteria:

1. Susceptible: organisms produce zones of 18 mm or greater, indicating that the tested organism is likely to respond to therapy.
2. Organisms that produce zones of 14 to 17 mm are expected to be susceptible if a high dosage (not to exceed 4 gm per day) is used or if the infection is confined to tissues and fluids (*e.g.*, urine), in which high antibiotic levels are attained.
3. Resistant: organisms produce zones of 13 mm or less, indicating that other therapy should be selected.

Organisms should be tested with the ceftriaxone disk, since ceftriaxone has been shown by *in vitro* tests to be active against certain strains found resistant to cephalosporin class disks.

Organisms having zones of less than 18 mm around the cephalothin disk are not necessarily of intermediate susceptibility or resistant to ceftriaxone.

Standardized procedures require use of control organisms. The 30-mcg ceftriaxone disk should give zone diameters between 29 and 35 mm, 22 and 28 mm and 17 and 23 mm for the reference strains *E coli* ATCC 25922, *S aureus* ATCC 25923 and *P aeruginosa* ATCC 27853, respectively.

*DILUTION TECHNIQUES*: Based on the pharmacokinetic profile of ceftriaxone, a bacterial isolate may be considered susceptible if the MIC value for ceftriaxone is not more than 16 mcg/ml. Organisms are considered resistant to ceftriaxone if the MIC is equal to or greater than 64 mcg/ml. Organisms having an MIC value of less than 64 mcg/ml, but greater than 16 mcg/ml, are expected to be susceptible if a high dosage (not to exceed 4 gm per day) is used or if the infection is confined to tissues and fluids (*e.g.*, urine), in which high antibiotic levels are attained.

*E coli* ATCC 25922, *S aureus* ATCC 25923 and *P aeruginosa* ATCC 27853 are also the recommended reference strains for controlling ceftriaxone dilution tests. Greater than 95% of MICs for the *E coli* strain should fall within the range of 0.016 to 0.5 mcg/ml. The range for the *S aureus* strain should be 1 to 2 mcg/ml, while for the *P aeruginosa* strain the range should be 8 to 64 mcg/ml.

**INDICATIONS AND USAGE**: Rocephin is indicated for the treatment of the following infections when caused by susceptible organisms:

*LOWER RESPIRATORY TRACT INFECTIONS* caused by *Strep pneumoniae, Streptococcus* species (excluding enterococci), *Staph aureus, H influenzae, H parainfluenzae, Klebsiella* species (including *K pneumoniae*), *E coli, E aerogenes, Proteus mirabilis* and *Serratia marcescens*.

*SKIN AND SKIN STRUCTURE INFECTIONS* caused by *Staph aureus, Staph epidermidis, Streptococcus* species (excluding enterococci), *E cloacae, Klebsiella* species (including *K pneumoniae*), *Proteus mirabilis* and *Pseudomonas aeruginosa*.

*URINARY TRACT INFECTIONS (complicated and uncomplicated)* caused by *E coli, Proteus mirabilis, Proteus vulgaris, M morganii* and *Klebsiella* species (including *K pneumoniae*).

*UNCOMPLICATED GONORRHEA (cervical/urethral and rectal)* caused by *Neisseria gonorrhoeae*, including both penicillinase and nonpenicillinase producing strains.

*PELVIC INFLAMMATORY DISEASE* caused by *N gonorrhoeae*.

*BACTERIAL SEPTICEMIA* caused by *Staph aureus, Strep pneumoniae, E coli, H influenzae* and *K pneumoniae*.

*BONE AND JOINT INFECTIONS* caused by *Staph aureus, Strep pneumoniae, Streptococcus* species (excluding enterococci), *E coli, P mirabilis, K pneumoniae* and *Enterobacter* species.

*INTRA-ABDOMINAL INFECTIONS* caused by *E coli* and *K pneumoniae*.

*MENINGITIS* caused by *H influenzae, N meningitidis* and *Strep pneumoniae*. Ceftriaxone has also been used successfully in a limited number of cases of meningitis and shunt infections caused by *Staph epidermidis* and *E coli*.

*PROPHYLAXIS*: The administration of a single dose of ceftriaxone preoperatively may reduce the incidence of postoperative infections in patients undergoing coronary artery bypass surgery.

Although ceftriaxone has been shown to have been as effective as cefazolin in the prevention of infection following coronary artery bypass surgery, no placebo-controlled trials have been conducted to evaluate any cephalosporin antibiotic in the prevention of infection following coronary artery bypass surgery.

*SUSCEPTIBILITY TESTING*: Before instituting treatment with Rocephin, appropriate specimens should be obtained for isolation of the causative organism and for determination of its susceptibility to the drug. Therapy may be instituted prior to obtaining results of susceptibility testing.

**CONTRAINDICATIONS**: Rocephin is contraindicated in patients with known allergy to the cephalosporin class of antibiotics.

**WARNINGS**: BEFORE THERAPY WITH ROCEPHIN IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE TO DETERMINE WHETHER THE PATIENT HAS HAD PREVIOUS HYPERSENSITIVITY REACTIONS TO CEPHALOSPORINS, PENICILLINS OR OTHER DRUGS. THIS PRODUCT SHOULD BE GIVEN CAUTIOUSLY TO PENICILLIN-SENSITIVE PATIENTS. ANTIBIOTICS SHOULD BE ADMINISTERED WITH CAUTION TO ANY PATIENT WHO HAS DEMONSTRATED SOME FORM OF ALLERGY, PARTICULARLY TO DRUGS. SERIOUS ACUTE HYPERSENSITIVITY REACTIONS MAY REQUIRE THE USE OF SUBCUTANEOUS EPINEPHRINE AND OTHER EMERGENCY MEASURES.

Pseudomembranous colitis has been reported with the use of cephalosporins (and other broad-spectrum antibiotics), therefore, it is important to consider its diagnosis in patients who develop diarrhea in association with antibiotic use.

**ROCEPHIN® (ceftriaxone sodium/Roche)**

Treatment with broad-spectrum antibiotics alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate a toxin produced by *Clostridium difficile* is one primary cause of antibiotic-associated colitis. Cholestyramine and colestipol resins have been shown to bind to the toxin *in vitro*.

Mild cases of colitis respond to drug discontinuance alone. Moderate to severe cases should be managed with fluid, electrolyte and protein supplementation as indicated.

When the colitis is not relieved by drug discontinuance or when it is severe, oral vancomycin is the treatment of choice for antibiotic-associated pseudomembranous colitis produced by *C difficile*. Other causes of colitis should also be considered.

**PRECAUTIONS**: *GENERAL*: Although transient elevations of BUN and serum creatinine have been observed at the recommended dosages, the nephrotoxic potential of Rocephin is similar to that of other cephalosporins.

Ceftriaxone is excreted via both biliary and renal excretion (see Clinical Pharmacology). Therefore, patients with renal failure normally require no adjustment in dosage when usual doses of Rocephin are administered, but concentrations of drug in the serum should be monitored periodically. If evidence of accumulation exists, dosage should be decreased accordingly.

Dosage adjustments should not be necessary in patients with hepatic dysfunction; however, in patients with both hepatic dysfunction and significant renal disease, Rocephin dosage should not exceed 2 gm daily without close monitoring of serum concentrations.

Alterations in prothrombin times have occurred rarely in patients treated with Rocephin. Patients with impaired vitamin K synthesis or low vitamin K stores (*e.g.*, chronic hepatic disease and malnutrition) may require monitoring of prothrombin time during Rocephin treatment. Vitamin K administration (10 mg weekly) may be necessary if the prothrombin time is prolonged before or during therapy.

Prolonged use of Rocephin may result in overgrowth of nonsusceptible organisms. Careful observation of the patient is essential. If superinfection occurs during therapy, appropriate measures should be taken.

Rocephin should be prescribed with caution in individuals with a history of gastrointestinal disease, especially colitis.

*CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY*: Carcinogenesis: Considering the maximum duration of treatment and the class of the compound, carcinogenicity studies with ceftriaxone in animals have not been performed. The maximum duration of animal toxicity studies was six months.

Mutagenesis: Genetic toxicology tests included the Ames test, a micronucleus test and a test for chromosomal aberrations in human lymphocytes cultured *in vitro* with ceftriaxone. Ceftriaxone showed no potential for mutagenic activity in these studies.

Impairment of Fertility: Ceftriaxone produced no impairment of fertility when given intravenously to rats at daily doses up to 586 mg/kg/day, approximately 20 times the recommended clinical dose of 2 gm/day.

*PREGNANCY*: Teratogenic Effects: Pregnancy Category B. Reproductive studies have been performed in mice and rats at doses up to 20 times the usual human dose and have no evidence of embryotoxicity, fetotoxicity or teratogenicity. In primates, no embryotoxicity or teratogenicity was demonstrated at a dose approximately three times the human dose.

There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproductive studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nonteratogenic Effects: In rats, in the Segment I (fertility and general reproduction) and Segment III (perinatal and postnatal) studies with intravenously administered ceftriaxone, no adverse effects were noted on various reproductive parameters during gestation and lactation, including postnatal growth, functional behavior and reproductive ability of the offspring, at doses of 586 mg/kg/day or less.

*NURSING MOTHERS*: Low concentrations of ceftriaxone are excreted in human milk. Caution should be exercised when Rocephin is administered to a nursing woman.

*PEDIATRIC USE*: Safety and effectiveness of Rocephin in neonates, infants and children have been established for the dosages described in the Dosage and Administration section.

**ADVERSE REACTIONS**: Rocephin is generally well tolerated. In clinical trials, the following adverse reactions, which were considered to be related to Rocephin therapy or of uncertain etiology, were observed:

*LOCAL REACTIONS*—pain, induration or tenderness at the site of injection (1%). Less frequently reported (less than 1%) was phlebitis after IV administration.

*HYPERSENSITIVITY*—rash (1.7%). Less frequently reported (less than 1%) were pruritus, fever or chills.

*HEMATOLOGIC*—eosinophilia (6%), thrombocytosis (5.1%) and leukopenia (2.1%). Less frequently reported (less than 1%) were anemia, neutropenia, lymphopenia, thrombocytopenia and prolongation of the prothrombin time.

*GASTROINTESTINAL*—diarrhea (2.7%). Less frequently reported (less than 1%) were nausea or vomiting and dysgeusia.

*HEPATIC*—elevations of SGOT (3.1%) or SGPT (3.3%). Less frequently reported (less than 1%) were elevations of alkaline phosphatase and bilirubin.

*RENAL*—elevations of the BUN (1.2%). Less frequently reported (less than 1%) were elevations of creatinine and the presence of casts in the urine.

*CENTRAL NERVOUS SYSTEM*—headache or dizziness were reported occasionally (less than 1%).

*GENITOURINARY*—moniliasis or vaginitis were reported occasionally (less than 1%).

*MISCELLANEOUS*—diaphoresis and flushing were reported occasionally (less than 1%).

Other rarely observed adverse reactions (less than 0.1%) include: leukocytosis, lymphocytosis, monocytosis, basophilia, a decrease in the prothrombin time, jaundice, glycosuria, hematuria, bronchospasm, serum sickness, abdominal pain, colitis, flatulence, dyspepsia, palpitations and epistaxis.

**DOSAGE AND ADMINISTRATION**: Rocephin may be administered intravenously or intramuscularly. The usual adult daily dose is 1 to 2 gm given once a day (or in equally divided doses twice a day) depending on the type and severity of the infection. The total daily dose should not exceed 4 grams.

For the treatment of serious miscellaneous infections in children, other than meningitis, the recommended total daily dose is 50 to 75 mg/kg (not to exceed 2 grams), given in divided doses every 12 hours.

Generally, Rocephin therapy should be continued for at least two days after the signs and symptoms of infection have disappeared. The usual duration is 4 to 14 days; in complicated infections longer therapy may be required.

In the treatment of meningitis, a daily dose of 100 mg/kg (not to exceed 4 grams), given in divided doses every 12 hours, should be administered with or without a loading dose of 75 mg/kg.

For the treatment of uncomplicated gonococcal infections, a single intramuscular dose of 250 mg is recommended.

For preoperative use (surgical prophylaxis), a single dose of 1 gm administered ½ to 2 hours before surgery is recommended.

When treating infections caused by *Streptococcus pyogenes*, therapy should be continued for at least ten days.

No dosage adjustment is necessary for patients with impairment of renal or hepatic function, however, blood levels should be monitored in patients with severe renal impairment (e.g., dialysis patients) and in patients with both renal and hepatic dysfunctions.

**HOW SUPPLIED**: Rocephin (ceftriaxone sodium/Roche) is supplied as a sterile crystalline powder in glass vials and piggyback bottles. The following packages are available:

Vials containing 250 mg equivalent of ceftriaxone. Boxes of 10 (NDC 0004-1962-01)

Vials containing 500 mg equivalent of ceftriaxone. Boxes of 10 (NDC 0004-1963-01)

Vials containing 1 gm equivalent of ceftriaxone. Boxes of 10 (NDC 0004-1964-01)

Piggyback bottles containing 1 gm equivalent of ceftriaxone. Boxes of 10 (NDC 0004-1964-03)

Vials containing 2 gm equivalent of ceftriaxone. Boxes of 10 (NDC 0004-1965-01)

Piggyback bottles containing 2 gm equivalent of ceftriaxone. Boxes of 10 (NDC 0004-1965-03)

Bulk pharmacy containers, containing 10 gm equivalent of ceftriaxone. Boxes of 1 (NDC 0004-1971-01)

NOT FOR DIRECT ADMINISTRATION.

Roche Laboratories
Division of Hoffmann-La Roche Inc.
Nutley, New Jersey 07110

# Mean,

Powerful against susceptible pathogens.*

# lean &

Easy on tight budgets.

# clean.

Gentle to patients (generally well tolerated).

The one antimicrobial that
belongs on every formulary.

Once-a-day

# Rocephin® ROCHE IV·IM

ceftriaxone sodium/Roche

* ROCEPHIN is indicated in the following infections: bacterial septicemia, bone and joint, intra-abdominal, lower respiratory tract, skin and skin structure, urinary tract, bacterial meningitis and gonorrhea. Please see summary of product information on adjacent page for indicated susceptible organisms.

Copyright © 1987 by Hoffmann-La Roche Inc. All rights reserved.

Please see adjacent page for summary of product information.